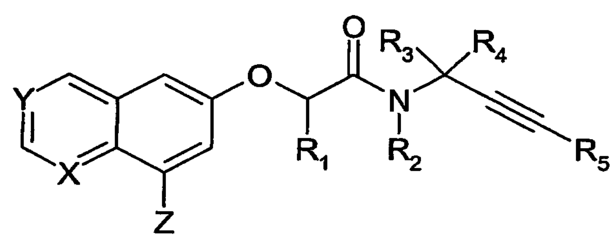
QUINOLIN-, ISOQUINOLIN-, AND QUINAZOLIN-OXYALKYLAMIDES AND THEIR USE AS FUNGICIDES

This invention relates to novel *N*-alkynyl-2-quinolin-(isoquinolin- and quinazolin-)oxyalkylamides, to processes for preparing them, to compositions containing them and to methods of using them to combat fungi, especially fungal infections of plants.

Various quinolin-8-oxyalkanecarboxylic acid derivatives are described as being useful as antidotes for herbicides or as herbicide safeners (see, for example, US 4,881,966, US 4,902,340 and US 5,380,852). Certain heteroaryloxy(thio)alkanoic acid amide derivatives are described in, for example, WO 99/33810, US 6090815 and JP 2001089453, together with their use as agricultural and horticultural fungicides. In addition, certain phenoxyalkanoic acid amide derivatives are described in, for example, US 4116677 and US 4168319, together with their use as herbicides and mildewicides.

According to the present invention, there is provided a compound of the general formula (1):



(1)

wherein

one of X and Y is N or N-oxide and the other is CR or both of X and Y are N;

Z is H, halo (e.g. fluoro, chloro, bromo or iodo), C_{1-6} alkyl optionally substituted with halo or C_{1-4} alkoxy, C_{3-6} cycloalkyl optionally substituted with halo or C_{1-4} alkoxy, C_{2-4} alkenyl optionally substituted with halo, C_{2-4} alkynyl optionally substituted with halo, C_{1-6} alkoxy optionally substituted with halo or C_{1-4} alkoxy, C_{2-4} alkenyloxy optionally substituted with halo (e.g. allyloxy), C_{2-4} alkynyloxy optionally substituted with halo (e.g. propargyloxy), cyano, nitro, C_{1-4} alkoxycarbonyl, $-OSO_2R'$, $S(O)_nR'$, -COR", -CONR"R"', -CR"=NOR', NR"R"', NR"COR', NR"CO_2R' where n is 0, 1 or 2, R' is C_{1-6} alkyl optionally substituted with halogen and R" and R"' are independently H or C_{1-6} alkyl or, in the case of -CONR"R"', may join to form a 5- or 6-membered ring containing a single nitrogen atom, saturated carbon atoms and optionally a single oxygen atom;

R is H, halo, C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkylthio, nitro, amino, mono- or di-(C_{1-6})alkylamino, mono- or di-(C_{2-6})alkenylamino, mono- or di-(C_{2-6})alkynylamino, formylamino, C_{1-4} alkyl(formyl)amino, C_{1-4} alkylcarbonylamino, C_{1-4} alkoxycarbonylamino, C_{1-4} alkyl(C_{1-4} alkylcarbonyl)amino, cyano, formyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, aminocarbonyl, mono- or di-(C_{1-4})alkylaminocarbonyl, carboxy, C_{1-4} alkylcarbonyloxy, aryl(C_{1-4})alkylcarbonyloxy, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl or C_{1-4} alkylsulphonyloxy;

R_1 is C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl in which the alkyl, alkenyl and alkynyl groups are optionally substituted on their terminal carbon atom with one, two or three halogen atoms (e.g. 2,2,2-trifluoroethyl), with a cyano group (e.g. cyanomethyl), with a C_{1-4} alkylcarbonyl group (e.g. acetylmethyl), with a C_{1-4} alkoxycarbonyl group (e.g. methoxycarbonylmethyl and methoxycarbonylethyl) or with a hydroxy group (e.g. hydroxymethyl), or

R_1 is alkoxyalkyl, alkylthioalkyl, alkylsulphinylalkyl or alkylsulphonylalkyl in which the total number of carbon atoms is 2 or 3 (e.g. methoxymethyl, methylthiomethyl, ethoxymethyl, 2-methoxyethyl and 2-methylthioethyl), or

R_1 is a straight-chain C_{1-4} alkoxy group (i.e. methoxy, ethoxy, *n*-propoxy and *n*-butoxy);

R_2 is H, C_{1-4} alkyl, C_{1-4} alkoxymethyl or benzyloxymethyl in which the phenyl ring of the benzyl moiety is optionally substituted with C_{1-4} alkoxy;

R_3 and R_4 are independently H, C_{1-3} alkyl, C_{2-3} alkenyl or C_{2-3} alkynyl provided that both are not H and that when both are other than H their combined total of carbon atoms does not exceed 4, or

R_3 and R_4 join with the carbon atom to which they are attached to form a 3 or 4 membered carbocyclic ring optionally containing one O, S or N atom and optionally substituted with halo or C_{1-4} alkyl; and

R_5 is H, C_{1-4} alkyl or C_{3-6} cycloalkyl in which the alkyl or cycloalkyl group is optionally substituted with halo, hydroxy, C_{1-6} alkoxy, cyano, C_{1-4} alkylcarbonyloxy, aminocarbonyloxy, mono- or di(C_{1-4})alkylaminocarbonyloxy, $-S(O)_n(C_{1-6})$alkyl where n is 0, 1 or 2, triazolyl (e.g. 1,2,4-triazol-1-yl), tri(C_{1-4})alkylsilyloxy, optionally substituted phenoxy, optionally substituted thienyloxy, optionally substituted benzyloxy or optionally substituted thienylmethoxy, or

R_5 is optionally substituted phenyl, optionally substituted thienyl or optionally substituted

benzyl,

in which the optionally substituted phenyl and thienyl rings of the R_5 values are optionally substituted with one, two or three substituents selected from halo, hydroxy, mercapto, C_{1-4} alkyl, C_{2-4}, alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{2-4} alkenyloxy, C_{2-4} alkynyloxy, halo (C_{1-4})alkyl, halo(C_{1-4})alkoxy, C_{1-4} alkylthio, halo(C_{1-4})alkylthio, hydroxy(C_{1-4})alkyl, C_{1-4} alkoxy(C_{1-4})alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl(C_{1-4})alkyl, phenoxy, benzyloxy, benzoyloxy, cyano, isocyano, thiocyanato, isothiocyanato, nitro, $-NR^mR^n$, $-NHCOR^m$, $-NHCONR^mR^n$, $-CONR^mR^n$, $-SO_2R^m$, $-OSO_2R^m$, $-COR^m$, $-CR^m{=}NR^n$ or $-N{=}CR^mR^n$, in which R^m and R^n are independently hydrogen, C_{1-4} alkyl, halo(C_{1-4})alkyl, C_{1-4} alkoxy, halo(C_{1-4})alkoxy, C_{1-4} alkylthio, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl(C_{1-4})alkyl, phenyl or benzyl, the phenyl and benzyl groups being optionally substituted with halogen, C_{1-4} alkyl or C_{1-4} alkoxy.

The compounds of the invention contain at least one asymmetric carbon atom (and at least two when R_3 and R_4 are different) and may exist as enantiomers (or as pairs of diastereoisomers) or as mixtures of such. However, these mixtures may be separated into individual isomers or isomer pairs, and this invention embraces such isomers and mixtures thereof in all proportions. It is to be expected that for any given compound, one isomer may be more fungicidally active than another.

Except where otherwise stated, alkyl groups and alkyl moieties of alkoxy, alkylthio, etc., suitably contain from 1 to 4 carbon atoms in the form of straight or branched chains. Examples are methyl, ethyl, *n*-and *iso*-propyl and *n*-, *sec*-, *iso*- and *tert*-butyl. Where alkyl moieties contain 5 or 6 carbon atoms, examples are *n*-pentyl and *n*-hexyl.

Alkenyl and alkynyl moieties also suitable contain from 2 to 4 carbon atoms in the form of straight or branched chains. Examples are allyl, ethynyl and propargyl.

Halo includes fluoro, chloro, bromo and iodo. Most commonly it is fluoro, chloro or bromo and usually fluoro or chloro.

Of particular interest are the compounds of the general formula (1) where X is N and Y is CR (quinolines). Also of interest are those compounds where X and Y are both N (quinazolines) and where Y is N and X is CR (isoquinolines).

Typically R is H, halo (for example, chloro or bromo) or cyano.

Z is typically H or halo (for example bromo).

Typically, R_1 is methyl, ethyl, *n*-propyl, 2,2,2-trifluoromethyl, cyanomethyl, acetylmethyl, methoxycarbonylmethyl, methoxycarbonylethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, methylthiomethyl, ethoxymethyl, 2-methoxyethyl, 2-methylthioethyl, methoxy, ethoxy, *n*-propoxy or *n*-butoxy. Ethyl is a preferred value of R_1 but also of particular interest are methoxy, ethoxy and methoxymethyl.

Typically R_2 is H and at least one, but preferably both of R_3 and R_4 are methyl.

When one of R_3 and R_4 is H, the other may be methyl, ethyl or *n*- or *iso*-propyl. When one of R_3 and R_4 is methyl, the other may be H or ethyl but is preferably also methyl. R_2 also includes C_{1-4} alkoxymethyl and benzyloxymethyl in which the phenyl ring of the benzyl group optionally carries an alkoxy substituent, e.g. a methoxy substituent. Such values of R_2 provide compounds of formula (1) that are believed to be pro-pesticidal compounds.

Typically R_5 is H, methyl, hydroxymethyl, methoxymethyl, 1-methoxyethyl, *tert*-butyldimethylsiloxymethyl, 3-cyanopropyl, 3-methoxypropyl, 3-(1,2,4-triazol-1-yl)-propyl, 3-methylthiopropyl, 3-methanesulphinylpropyl or 3-methanesulphonylpropyl. Of particular interest are compounds where R_5 is methyl, methoxymethyl or cyanopropyl.

In one aspect the invention provides a compound of the general formula (1) wherein X, Y, Z, R_1, R_2, R_3, R_4 and R_5 are as defined above except that R_5 is other than H.

In another aspect, the invention provides a compound of the general formula (1) wherein

one of X and Y is N and the other is CR or both of X and Y are N;

Z is H;

R is H, halo, C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkylthio, nitro, amino, mono- or di-(C_{1-6})alkylamino, mono- or di-(C_{2-6})alkenylamino, mono- or di-(C_{2-6})alkynylamino, formylamino, C_{1-4} alkyl(formyl)amino, C_{1-4} alkylcarbonylamino, C_{1-4} alkyl(C_{1-4} alkylcarbonyl)amino, cyano, formyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, aminocarbonyl, mono- or di-(C_{1-4})alkylaminocarbonyl, carboxy, C_{1-4} alkylcarbonyloxy, aryl(C_{1-4})alkylcarbonyloxy, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl or C_{1-4} alkylsulphonyloxy;

R_1 is C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl in which the alkyl, alkenyl and alkynyl groups are optionally substituted on their terminal carbon atom with one, two or three

halogen atoms, with a cyano group, with a C_{1-4} alkylcarbonyl group, with a C_{1-4} alkoxycarbonyl group or with a hydroxy group, or

R_1 is alkoxyalkyl, alkylthioalkyl, alkylsulphinylalkyl or alkylsulphonylalkyl in which the total number of carbon atoms is 2 or 3, or

R_1 is a straight-chain C_{1-4} alkoxy group;

R_2 is H, C_{1-4} alkyl, C_{1-4} alkoxymethyl or benzyloxymethyl in which the phenyl ring of the benzyl moiety is optionally substituted with C_{1-4} alkoxy;

R_3 and R_4 are independently H, C_{1-3} alkyl, C_{2-3} alkenyl or C_{2-3} alkynyl provided that both are not H and that when both are other than H their combined total of carbon atoms does not exceed 4, or

R_3 and R_4 join with the carbon atom to which they are attached to form a 3 or 4 membered carbocyclic ring optionally containing one O, S or N atom and optionally substituted with halo or C_{1-4} alkyl; and

R_5 is H, C_{1-4} alkyl or C_{3-6} cycloalkyl in which the alkyl or cycloalkyl group is optionally substituted with halo, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, cyano, C_{1-4} alkylcarbonyloxy, aminocarbonyloxy or mono- or di(C_{1-4})alkylaminocarbonyloxy, tri(C_{1-4})alkylsilyloxy, optionally substituted phenoxy, optionally substituted thienyloxy, optionally substituted benzyloxy or optionally substituted thienylmethoxy, or

R_5 is optionally substituted phenyl, optionally substituted thienyl or optionally substituted benzyl,

in which the optionally substituted phenyl and thienyl rings of the R_5 values are optionally substituted with one, two or three substituents selected from halo, hydroxy, mercapto, C_{1-4} alkyl, C_{2-4}, alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{2-4} alkenyloxy, C_{2-4} alkynyloxy, halo (C_{1-4})alkyl, halo(C_{1-4})alkoxy, C_{1-4} alkylthio, halo(C_{1-4})alkylthio, hydroxy(C_{1-4})alkyl, C_{1-4} alkoxy(C_{1-4})alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl(C_{1-4})alkyl, phenoxy, benzyloxy, benzoyloxy, cyano, isocyano, thiocyanato, isothiocyanato, nitro, $-NR^mR^n$, $-NHCOR^m$, $-NHCONR^mR^n$, $-CONR^mR^n$, $-SO_2R^m$, $-OSO_2R^m$, $-COR^m$, $-CR^m{=}NR^n$ or $-N{=}CR^mR^n$, in which R^m and R^n are independently hydrogen, C_{1-4} alkyl, halo(C_{1-4})alkyl, C_{1-4} alkoxy, halo(C_{1-4})alkoxy, C_{1-4} alkylthio, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl(C_{1-4})alkyl, phenyl or benzyl, the phenyl and benzyl groups being optionally substituted with halogen, C_{1-4} alkyl or C_{1-4} alkoxy.

In another aspect, the invention provides a compound of the general formula (1) wherein one of X and Y is N and the other is CR or both of X and Y are N; Z is H; R is H, halo or cyano R_1 is methyl, ethyl, *n*-propyl, 2,2,2-trifluoromethyl, cyanomethyl, acetylmethyl, methoxycarbonylmethyl, methoxycarbonylethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, methylthiomethyl, ethoxymethyl, 2-methoxyethyl, methoxy, ethoxy, *n*-propoxy, *n*-butoxy; R_2 is H; R_3 and R_4 are both methyl; and R_5 is H, methyl, hydroxymethyl, methoxymethyl, 1-methoxyethyl, *tert*-butyldimethyl-siloxymethyl, 3-cyanopropyl, 3-methoxypropyl, 3-(1,2,4-triazol-1-yl)propyl, 3-methyl-thiopropyl, 3-methanesulphinylpropyl or 3-methanesulphonylpropyl. Preferably R_1 is ethyl, methoxy, ethoxy or methoxymethyl, especially ethyl. Preferably R_5 is methyl, methoxymethyl or 3-cyanopropyl.

Compounds that form part of the invention are illustrated in Tables 1 to 152 below.

The compounds in Table 1 are of the general formula (1) where X is N, Y is CH, Z is H, R_1 is ethyl, R_2 is H, R_3 and R_4 are both methyl and R_5 has the values given in the table.

Table 1

Compound No.	**R_5**
1	H
2	CH_3
3	C_2H_5
4	*n*-C_3H_7
5	*i*-C_3H_7
6	*n*-C_4H_9
7	*sec*-C_4H_9
8	*iso*-C_4H_9
9	*tert*-C_4H_9
10	$HOCH_2$
11	HOC_2H_4
12	CH_3OCH_2
13	$CH_3OCH_2CH_2$

14	$C_2H_5OCH_2$
15	$CH_3(CH_3O)CH$
16	n-$C_3H_7OCH_2$
17	n-$C_3H_7OC_2H_4$
18	t-$C_4H_9OCH_2$
19	t-$C_4H_9OC_2H_4$
20	CH_3SCH_2
21	$CH_3SC_2H_4$
22	$C_2H_5SCH_2$
23	$C_2H_5SC_2H_4$
24	n-$C_3H_7SCH_2$
25	n-$C_4H_9SCH_2$
26	$C_6H_5OCH_2$
27	$C_6H_5OC_2H_4$
28	4-t-C_4H_9-$C_6H_4OCH_2$
29	4-F-$C_6H_4OCH_2$
30	4-Cl-$C_6H_4OCH_2$
31	4-CH_3-$C_6H_4OCH_2$
32	4-Br-$C_6H_4OCH_2$
33	2-F-$C_6H_4OCH_2$
34	3,4-Cl_2-$C_6H_3OCH_2$
35	3-CF_3-$C_6H_4OCH_2$
36	3,5-Cl_2-$C_6H_3OCH_2$
37	4-CF_3O-$C_6H_5OCH_2$
38	2-CF_3-$C_6H_4OCH_2$
39	4-CF_3-$C_6H_4OCH_2$
40	2-Br-$C_6H_4OCH_2$
41	2-Cl-$C_6H_4OCH_2$
42	2-CH_3-4-Cl-$C_6H_3OCH_2$
43	2-$CH_3$5-F-$C_6H_3OCH_2$
44	3-Cl-$C_6H_4OCH_2$

45	thien-2-yl-OCH_2
46	thien-3-yl-OCH_2
47	$C_6H_5CH_2OCH_2$
48	thien-2-yl-CH_2OCH_2
49	thien-3-yl-CH_2OCH_2
50	*tert*-$C_4H_9(CH_3)_2SiOCH_2$
51	*tert*-$C_4H_9(CH_3)_2SiOC_2H_4$
52	C_6H_5
53	4-*t*-C_4H_9-C_6H_4
54	4-F-C_6H_4
55	4-Cl-C_6H_4
56	4-CH_3-C_6H_4
57	4-Br-C_6H_4
58	3CH_3CO-C_6H_4
59	3,4-Cl_2-C_6H_3
60	3-CF_3-C_6H_4
61	3,5-Cl_2-C_6H_3
62	4-CF_3O-C_6H_4
63	2-CF_3-C_6H_4
64	4-CF_3-C_6H_4
65	2-Br-C_6H_4
66	2-Cl-C_6H_4
67	2-CH_3-4-Cl-C_6H_3
68	2-$CH_3$5-F-C_6H_3
69	3-Cl-C_6H_4
70	thien-2-yl
71	thien-3-yl
72	$C_6H_5CH_2$
73	4-*t*-C_4H_9-$C_6H_4CH_2$
74	4-F-$C_6H_4CH_2$
75	4-Cl-$C_6H_4CH_2$

76	4-CH_3-$C_6H_4CH_2$
77	4-Br-$C_6H_4CH_2$
78	2-F-$C_6H_4CH_2$
79	3,4-Cl_2-$C_6H_3CH_2$
80	3-CF_3-$C_6H_4CH_2$
81	3,5-Cl_2-$C_6H_3CH_2$
82	4-CF_3O-$C_6H_5CH_2$
83	2-CF_3-$C_6H_4CH_2$
84	4-CF_3-$C_6H_4CH_2$
85	2-Br-$C_6H_4CH_2$
86	2-Cl-$C_6H_4CH_2$
87	2-CH_3-4-Cl-$C_6H_3CH_2$
88	2-$CH_3$5-F-$C_6H_3CH_2$
89	3-Cl-$C_6H_4CH_2$
90	$NC(CH_2)_2CH_2$
91	$Cl(CH_2)_2CH_2$
92	$F(CH_2)_2CH_2$
93	$NCCH_2CH_2$
94	$ClCH_2CH_2$
95	FCH_2CH_2
96	$CH_3SO(CH_2)_2CH_2$
97	$CH_3SO_2(CH_2)_2CH_2$
98	1,2,4-triazol-1-yl-$(CH_2)_2CH_2$
99	$CH_3SOCH_2CH_2$
100	$CH_3SO_2CH_2CH_2$
101	1,2,4-triazol-1-yl-CH_2CH_2

Table 2

Table 2 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is methyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 2 is the same as compound 1 of Table 1 except

that in compound 1 of Table 2 R_1 is methyl instead of ethyl. Similarly, compounds 2 to 101 of Table 2 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 2 R_1 is methyl instead of ethyl.

Table 3

Table 3 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is *n*-propyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 3 is the same as compound 1 of Table 1 except that in compound 1 of Table 3 R_1 is *n*-propyl instead of ethyl. Similarly, compounds 2 to 101 of Table 3 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 3 R_1 is *n*-propyl instead of ethyl.

Table 4

Table 4 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is 2,2,2-trifluoroethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 4 is the same as compound 1 of Table 1 except that in compound 1 of Table 4 R_1 is 2,2,2-trifluoroethyl instead of ethyl. Similarly, compounds 2 to 101 of Table 4 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 4 R_1 is 2,2,2-trifluoroethyl instead of ethyl.

Table 5

Table 5 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is cyanomethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 5 is the same as compound 1 of Table 1 except that in compound 1 of Table 5 R_1 is cyanomethyl instead of ethyl. Similarly, compounds 2 to 101 of Table 5 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 5 R_1 is cyanomethyl instead of ethyl.

Table 6

Table 6 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is acetylmethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 6 is the same as compound 1 of Table 1 except that in compound 1 of Table 6 R_1 is acetylmethyl instead of ethyl. Similarly, compounds 2 to 101 of Table 6 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 2 R_1 is acetylmethyl instead of ethyl.

Table 7

Table 7 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is methoxycarbonylmethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 7 is the same as compound 1 of Table 1 except that in compound 1 of Table 7 R_1 is methoxycarbonylmethyl instead of ethyl. Similarly, compounds 2 to 101 of Table 7 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 7 R_1 is methoxycarbonyl-methyl instead of ethyl.

Table 8

Table 8 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is methoxycarbonylethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 8 is the same as compound 1 of Table 1 except that in compound 1 of Table 8 R_1 is methoxycarbonylethyl instead of ethyl. Similarly, compounds 2 to 101 of Table 8 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 8 R_1 is methoxycarbonylethyl instead of ethyl.

Table 9

Table 9 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is hydroxymethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 9 is the same as compound 1 of Table 1 except that in compound 1 of Table 9 R_1 is hydroxymethyl instead of ethyl. Similarly, compounds 2 to 101 of Table 9 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 9 R_1 is hydroxymethyl instead of ethyl.

Table 10

Table 10 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is hydroxethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 10 is the same as compound 1 of Table 1 except that in compound 1 of Table 10 R_1 is hydroxyethyl instead of ethyl. Similarly, compounds 2 to 101 of Table 10 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 10 R_1 is hydroxyethyl instead of ethyl.

Table 11

Table 11 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is methoxymethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 11 is the same as compound 1 of Table 1 except that in compound 1 of Table 11 R_1 is methoxymethyl instead of ethyl. Similarly, compounds 2 to 101 of Table 11 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 11 R_1 is methoxymethyl instead of ethyl.

Table 12

Table 12 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is methylthiomethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 12 is the same as compound 1 of Table 1 except that in compound 1 of Table 12 R_1 is methylthiomethyl instead of ethyl. Similarly, compounds 2 to 101 of Table 12 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 12 R_1 is methylthiomethyl instead of ethyl.

Table 13

Table 13 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is ethoxymethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 13 is the same as compound 1 of Table 1 except that in compound 1 of Table 13 R_1 is ethoxymethyl instead of ethyl. Similarly, compounds 2 to 101 of Table 13 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 13 R_1 is ethoxymethyl instead of ethyl.

Table 14

Table 14 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is 2-methoxyethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 14 is the same as compound 1 of Table 1 except that in compound 1 of Table 14 R_1 is 2-methoxyethyl instead of ethyl. Similarly, compounds 2 to 101 of Table 14 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 14 R_1 is 2-methoxyethyl instead of ethyl.

Table 15

Table 15 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is 2-methythioethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 15 is the same as compound 1 of Table 1 except that in compound 1 of Table 15 R_1 is 2-methythioethyl instead of ethyl. Similarly, compounds 2 to 101 of Table 15 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 15 R_1 is 2-methythioethyl instead of ethyl.

Table 16

Table 16 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is methoxy, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 16 is the same as compound 1 of Table 1 except that in compound 1 of Table 16 R_1 is methoxy instead of ethyl. Similarly, compounds 2 to 101 of Table 16 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 16 R_1 is methoxy instead of ethyl.

Table 17

Table 17 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is ethoxy, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 17 is the same as compound 1 of Table 1 except that in compound 1 of Table 17 R_1 is ethoxy instead of ethyl. Similarly, compounds 2 to 101 of Table 17 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 17 R_1 is ethoxy instead of ethyl.

Table 18

Table 18 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is *n*-propoxy, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 18 is the same as compound 1 of Table 1 except that in compound 1 of Table 18 R_1 is *n*-propoxy instead of ethyl. Similarly, compounds 2 to 101 of Table 18 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 18 R_1 is *n*-propoxy instead of ethyl.

Table 19

Table 19 consists of 101 compounds of the general formula (1), where X is N, Y is CH, Z is H, R_1 is *n*-butoxy, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values

listed in Table 1. Thus compound 1 of Table 19 is the same as compound 1 of Table 1 except that in compound 1 of Table 19 R_1 is *n*-butoxy instead of ethyl. Similarly, compounds 2 to 101 of Table 19 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 19 R_1 is *n*-butoxy instead of ethyl.

Table 20

Table 20 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is ethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 20 is the same as compound 1 of Table 1 except that in compound 1 of Table 20 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 20 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 20 Y is N instead of CH.

Table 21

Table 21 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is methyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 21 is the same as compound 1 of Table 2 except that in compound 1 of Table 21 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 21 are the same as compounds 2 to 101 of Table 2, respectively, except that in the compounds of Table 21 Y is N instead of CH.

Table 22

Table 22 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is *n*-propyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 22 is the same as compound 1 of Table 3 except that in compound 1 of Table 22 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 22 are the same as compounds 2 to 101 of Table 3, respectively, except that in the compounds of Table 22 Y is N instead of CH.

Table 23

Table 23 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is 2,2,2-trifluoroethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 23 is the same as compound 1 of Table 4 except that in compound 1 of Table 23 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 23 are the same as compounds 2 to 101 of Table 4, respectively, except that in the compounds of Table 23 Y is N instead of CH.

Table 24

Table 24 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is cyanomethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 24 is the same as compound 1 of Table 5 except that in compound 1 of Table 24 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 24 are the same as compounds 2 to 101 of Table 5, respectively, except that in the compounds of Table 24 Y is N instead of CH.

Table 25

Table 25 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is acetylmethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 25 is the same as compound 1 of Table 6 except that in compound 1 of Table 25 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 25 are the same as compounds 2 to 101 of Table 6, respectively, except that in the compounds of Table 25 Y is N instead of CH.

Table 26

Table 26 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is methoxycarbonylmethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 26 is the same as compound 1 of Table 7 except that in compound 1 of Table 26 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 26 are the same as compounds 2 to 101 of Table 7, respectively, except that in the compounds of Table 26 Y is N instead of CH.

Table 27

Table 27 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is methoxycarbonylethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 27 is the same as compound 1 of Table 8 except that in compound 1 of Table 27 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 27 are the same as compounds 2 to 101 of Table 8, respectively, except that in the compounds of Table 27 Y is N instead of CH.

Table 28

Table 28 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is hydroxymethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 28 is the same as compound 1 of

Table 9 except that in compound 1 of Table 28 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 28 are the same as compounds 2 to 101 of Table 9, respectively, except that in the compounds of Table 28 Y is N instead of CH.

Table 29

Table 29 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is hydroxethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 29 is the same as compound 1 of Table 10 except that in compound 1 of Table 29 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 29 are the same as compounds 2 to 101 of Table 10, respectively, except that in the compounds of Table 29 Y is N instead of CH.

Table 30

Table 30 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is methoxymethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 30 is the same as compound 1 of Table 11 except that in compound 1 of Table 30 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 30 are the same as compounds 2 to 101 of Table 11, respectively, except that in the compounds of Table 30 Y is N instead of CH.

Table 31

Table 31 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is methylthiomethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 31 is the same as compound 1 of Table 12 except that in compound 1 of Table 31 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 31 are the same as compounds 2 to 101 of Table 12, respectively, except that in the compounds of Table 31 Y is N instead of CH.

Table 32

Table 32 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is ethoxymethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 32 is the same as compound 1 of Table 13 except that in compound 1 of Table 32 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 32 are the same as compounds 2 to 101 of Table 13, respectively, except that in the compounds of Table 32 Y is N instead of CH.

Table 33

Table 33 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is 2-methoxyethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 33 is the same as compound 1 of Table 14 except that in compound 1 of Table 33 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 33 are the same as compounds 2 to 101 of Table 14, respectively, except that in the compounds of Table 33 Y is N instead of CH.

Table 34

Table 34 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is 2-methylthioethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 34 is the same as compound 1 of Table 15 except that in compound 1 of Table 34 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 34 are the same as compounds 2 to 101 of Table 15, respectively, except that in the compounds of Table 34 Y is N instead of CH.

Table 35

Table 35 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is methoxy, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 35 is the same as compound 1 of Table 16 except that in compound 1 of Table 35 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 35 are the same as compounds 2 to 101 of Table 16, respectively, except that in the compounds of Table 35 Y is N instead of CH.

Table 36

Table 36 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is ethoxy, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 36 is the same as compound 1 of Table 17 except that in compound 1 of Table 36 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 36 are the same as compounds 2 to 101 of Table 17, respectively, except that in the compounds of Table 36 Y is N instead of CH.

Table 37

Table 37 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is *n*-propoxy, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 37 is the same as compound 1 of

Table 18 except that in compound 1 of Table 37 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 37 are the same as compounds 2 to 101 of Table 18, respectively, except that in the compounds of Table 37 Y is N instead of CH.

Table 38

Table 38 consists of 101 compounds of the general formula (1), where X and Y are both N, Z is H, R_1 is *n*-butoxy, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 38 is the same as compound 1 of Table 19 except that in compound 1 of Table 38 Y is N instead of CH. Similarly, compounds 2 to 101 of Table 38 are the same as compounds 2 to 101 of Table 19, respectively, except that in the compounds of Table 38 Y is N instead of CH.

Table 39

Table 39 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is ethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 39 is the same as compound 1 of Table 1 except that in compound 1 of Table 39 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 39 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 39 Y is N instead of CH and X is CH instead of N.

Table 40

Table 40 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is methyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 40 is the same as compound 1 of Table 2 except that in compound 1 of Table 40 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 40 are the same as compounds 2 to 101 of Table 2, respectively, except that in the compounds of Table 40 Y is N instead of CH and X is CH instead of N.

Table 41

Table 41 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is *n*-propyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 41 is the same as compound 1 of Table 3 except that in compound 1 of Table 41 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 41 are the same as compounds 2 to 101 of Table

3, respectively, except that in the compounds of Table 41 Y is N instead of CH and X is CH instead of N.

Table 42

Table 42 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is 2,2,2-trifluoroethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 42 is the same as compound 1 of Table 4 except that in compound 1 of Table 42 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 42 are the same as compounds 2 to 101 of Table 4, respectively, except that in the compounds of Table 42 Y is N instead of CH and X is CH instead of N.

Table 43

Table 43 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is cyanomethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 43 is the same as compound 1 of Table 5 except that in compound 1 of Table 43 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 43 are the same as compounds 2 to 101 of Table 5, respectively, except that in the compounds of Table 43 Y is N instead of CH and X is CH instead of N.

Table 44

Table 44 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is acetylmethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 44 is the same as compound 1 of Table 6 except that in compound 1 of Table 44 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 44 are the same as compounds 2 to 101 of Table 6, respectively, except that in the compounds of Table 44 Y is N instead of CH and X is CH instead of N.

Table 45

Table 45 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is methoxycarbonylmethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 45 is the same as compound 1 of Table 7 except that in compound 1 of Table 45 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 45 are the same as compounds 2 to 101 of

Table 7, respectively, except that in the compounds of Table 45 Y is N instead of CH and X is CH instead of N.

Table 46

Table 46 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is methoxycarbonylethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 46 is the same as compound 1 of Table 8 except that in compound 1 of Table 46 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 46 are the same as compounds 2 to 101 of Table 8, respectively, except that in the compounds of Table 46 Y is N instead of CH and X is CH instead of N.

Table 47

Table 47 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is hydroxymethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 47 is the same as compound 1 of Table 9 except that in compound 1 of Table 47 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 47 are the same as compounds 2 to 101 of Table 9, respectively, except that in the compounds of Table 47 Y is N instead of CH and X is CH instead of N.

Table 48

Table 48 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is hydroxethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 48 is the same as compound 1 of Table 10 except that in compound 1 of Table 48 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 48 are the same as compounds 2 to 101 of Table 10, respectively, except that in the compounds of Table 48 Y is N instead of CH and X is CH instead of N.

Table 49

Table 49 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is methoxymethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 49 is the same as compound 1 of Table 11 except that in compound 1 of Table 49 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 49 are the same as compounds 2 to

101 of Table 11, respectively, except that in the compounds of Table 49 Y is N instead of CH and X is CH instead of N.

Table 50

Table 50 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is methylthiomethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 50 is the same as compound 1 of Table 12 except that in compound 1 of Table 50 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 50 are the same as compounds 2 to 101 of Table 12, respectively, except that in the compounds of Table 50 Y is N instead of CH and X is CH instead of N.

Table 51

Table 51 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is ethoxymethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 51 is the same as compound 1 of Table 13 except that in compound 1 of Table 51 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 51 are the same as compounds 2 to 101 of Table 13, respectively, except that in the compounds of Table 51 Y is N instead of CH and X is CH instead of N.

Table 52

Table 52 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is 2-methoxyethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 52 is the same as compound 1 of Table 14 except that in compound 1 of Table 52 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 52 are the same as compounds 2 to 101 of Table 14, respectively, except that in the compounds of Table 52 Y is N instead of CH and X is CH instead of N.

Table 53

Table 53 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is 2-methylthioethyl, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 53 is the same as compound 1 of Table 15 except that in compound 1 of Table 53 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 53 are the same as compounds 2 to

101 of Table 15, respectively, except that in the compounds of Table 53 Y is N instead of CH and X is CH instead of N.

Table 54

Table 54 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is methoxy, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 54 is the same as compound 1 of Table 16 except that in compound 1 of Table 54 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 54 are the same as compounds 2 to 101 of Table 1, respectively, except that in the compounds of Table 16 Y is N instead of CH and X is CH instead of N.

Table 55

Table 55 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is ethoxy, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 55 is the same as compound 1 of Table 17 except that in compound 1 of Table 55 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 55 are the same as compounds 2 to 101 of Table 17, respectively, except that in the compounds of Table 55 Y is N instead of CH and X is CH instead of N.

Table 56

Table 56 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is *n*-propoxy, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 56 is the same as compound 1 of Table 18 except that in compound 1 of Table 56 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 56 are the same as compounds 2 to 101 of Table 18, respectively, except that in the compounds of Table 56 Y is N instead of CH and X is CH instead of N.

Table 57

Table 57 consists of 101 compounds of the general formula (1), where X is CH, Y is N, Z is H, R_1 is *n*-butoxy, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. Thus compound 1 of Table 57 is the same as compound 1 of Table 19 except that in compound 1 of Table 57 Y is N instead of CH and X is CH instead of N. Similarly, compounds 2 to 101 of Table 57 are the same as compounds 2 to 101 of Table

19, respectively, except that in the compounds of Table 57 Y is N instead of CH and X is CH instead of N.

Tables 58 to 76

Tables 58 to 76 each consist of 101 compounds of the general formula (1) where X is N, Y is CCl, Z is H, R_1 is as defined in Tables 1 to 19, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. These tables are the same as Tables 1 to 19 (i.e. Table 58 is the same as Table 1, Table 59 is the same as Table 2, etc.), except that in each of Tables 58 to 76 Y is CCl instead of CH. R_1 in Tables 58 to 76 has the value corresponding to its value in Tables 1 to 19, respectively (i.e. Table 58 has the same value of R_1 as Table 1, Table 59 has the same value of R_1 as Table 2, etc.).

Tables 77 to 95

Tables 77 to 95 each consist of 101 compounds of the general formula (1) where X is N, Y is CBr, Z is H, R_1 is as defined in Tables 1 to 19, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. These tables are the same as Tables 1 to 19 (i.e. Table 77 is the same as Table 1, Table 78 is the same as Table 2, etc.), except that in each of Tables 77 to 95 Y is CBr instead of CH. R_1 in Tables 77 to 95 has the value corresponding to its value in Tables 1 to 19, respectively (i.e. Table 77 has the same value of R_1 as Table 1, Table 78 has the same value of R_1 as Table 2, etc.).

Tables 96 to 114

Tables 96 to 114 each consist of 101 compounds of the general formula (1) where X is N, Y is CCN, Z is H, R_1 is as defined in Tables 1 to 19, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. These tables are the same as Tables 1 to 19 (i.e. Table 96 is the same as Table 1, Table 97 is the same as Table 2, etc.), except that in each of Tables 96 to 114 Y is CCN instead of CH. R_1 in Tables 96 to 114 has the value corresponding to its value in Tables 1 to 19, respectively (i.e. Table 96 has the same value of R_1 as Table 1, Table 97 has the same value of R_1 as Table 2, etc.).

Tables 115 to 133

Tables 115 to 133 each consist of 101 compounds of the general formula (1) where X is N, Y is CBr, Z is Br, R_1 is as defined in Tables 1 to 19, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. These tables are the same as Tables 1 to 19 (i.e. Table 115 is the same as Table 1, Table 116 is the same as Table 2, etc.), except that in each of Tables 115 to 133 Y is CBr instead of CH and Z is Br instead of H.

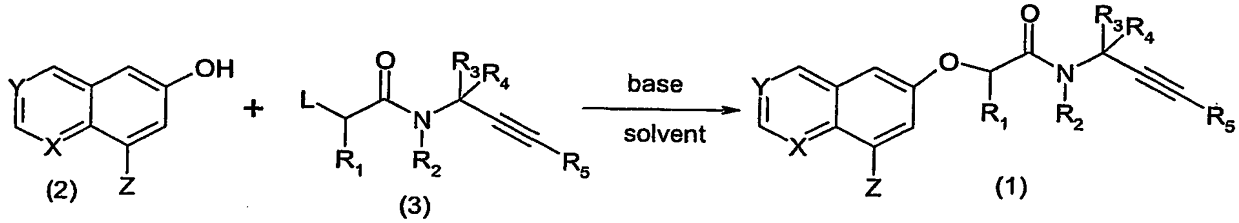
R_1 in Tables 115 to 133 has the value corresponding to its value in Tables 1 to 19, respectively (i.e. Table 115 has the same value of R_1 as Table 1, Table 116 has the same value of R_1 as Table 2, etc.).

<u>Tables 134 to 152</u>

Tables 134 to 152 each consist of 101 compounds of the general formula (1) where X is N-oxide, Y is CH, Z is H, R_1 is as defined in Tables 1 to 19, R_2 is hydrogen, R_3 and R_4 are both methyl and R_5 has the values listed in Table 1. These tables are the same as Tables 1 to 19 (i.e. Table 134 is the same as Table 1, Table 135 is the same as Table 2, etc.), except that in each of Tables 134 to 152 X is the N-oxide instead of N. R_1 in Tables 134 to 152 has the value corresponding to its value in Tables 1 to 19, respectively (i.e. Table 134 has the same value of R_1 as Table 1, Table 135 has the same value of R_1 as Table 2, etc.).

The compounds of formula (1) may be prepared as outlined in Schemes 1 to 10 below in which X, Y, Z, R_1, R_2, R_3, R_4 and R_5 have the meanings given above, R is C_{1-4} alkyl, R_6 is straight-chain C_{1-4} alkyl, R_7 and R_8 are independently H or C_{1-4} alkyl, L is a leaving group such as a halide, for example iodide, an alkyl or aryl sulphonyloxy group, for example methylsulphonyloxy and tosyloxy or a triflate, Hal is halogen, R_a is hydrogen or C_{1-3} alkyl, R_b is hydrogen or C_{1-3} alkyl, provided that the total number of carbon atoms in R_a and R_b do not exceed three, R_c is C_{1-6} alkyl, optionally substituted benzyl or optionally substituted thienylmethyl and R_d has the meaning ascribed to it in the text.

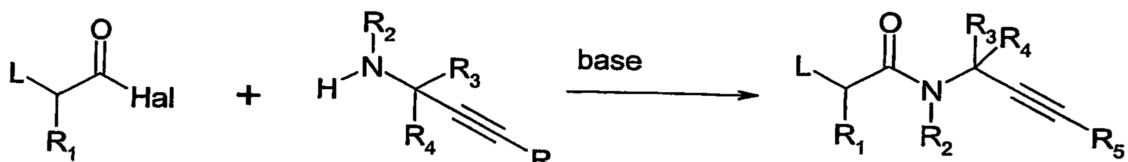
As shown in Scheme 1, the compounds of general formula (1) may be prepared by reacting a compound of the general formula (2) with a compound of the general formula (3) in the presence of a base in a suitable solvent. Typical solvents include *N,N*-dimethyl-formamide and *N*-methylpyrrolidin-2-one. Suitable bases include potassium carbonate, sodium hydride or di*iso*propylethylamine.



Scheme 1

As shown in Scheme 2, compounds of the general formula (3) may be prepared by reacting an amine of the general formula (5) with an acid halide of the general formula (4), or the corresponding acid anhydride, in the presence of a suitable inorganic or organic base, such as potassium carbonate or di*iso*propylethylamine, in a solvent such as dichloromethane or tetrahydrofuran.

Scheme 2



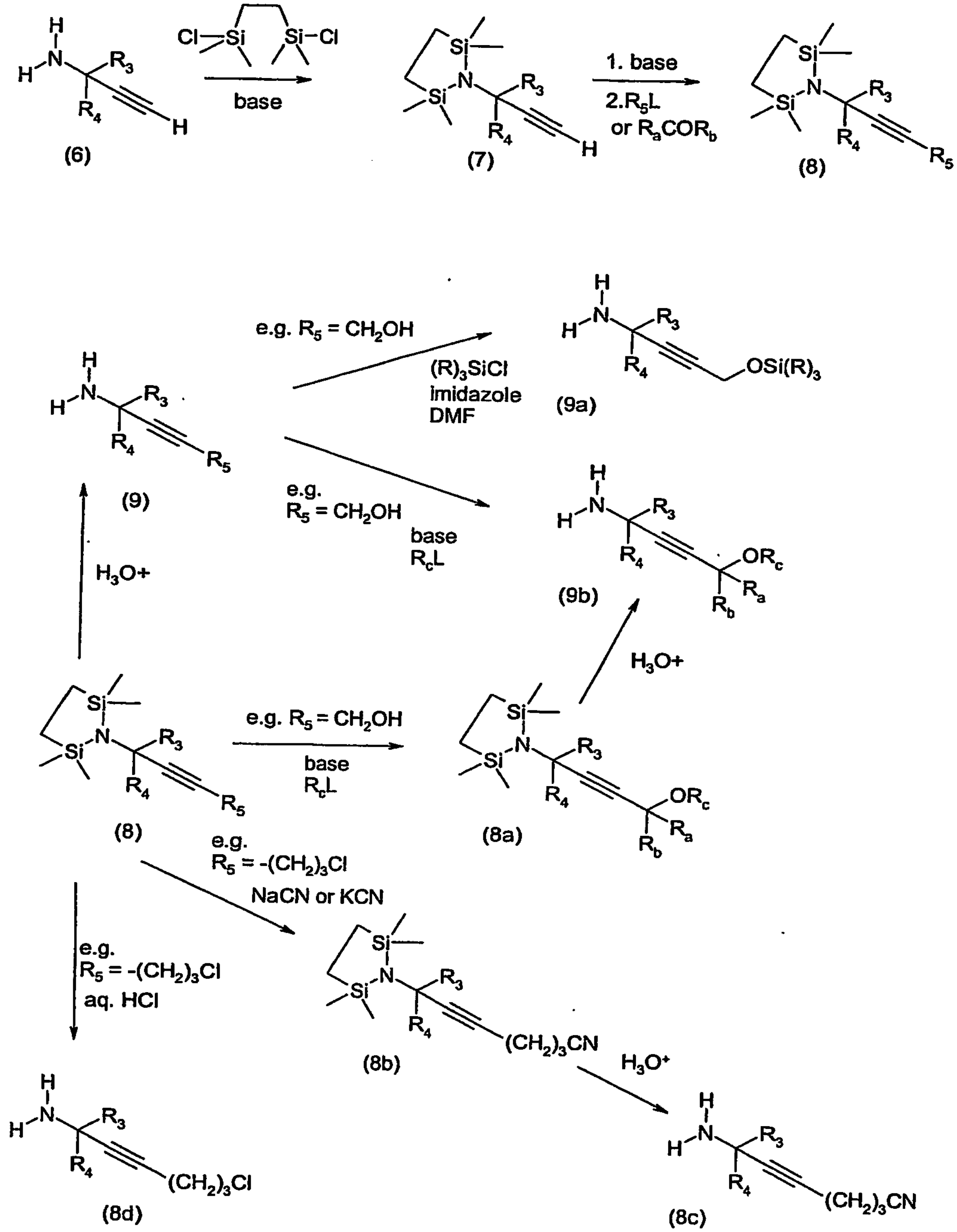
(4) (5) (3)

As shown in Scheme 3, amines of the general formula (5), wherein R_2 is H, correspond to amines of the general formula (9) and may be prepared by alkylation of a silyl-protected aminoalkyne of the general formula (7) using a suitable base, such as *n*-butyl lithium, followed by reaction with a suitable alkylating reagent R_5L, such as an alkyl iodide, for example, methyl iodide, to form an alkylated compound of the general formula (8). In a similar procedure, a silyl-protected aminoalkyne of the general formula (7) may be reacted with a carbonyl derivative R_aCOR_b, for example formaldehyde, using a suitable base, such as *n*-butyl lithium, to provide an aminoalkyne (8) containing a hydroxyalkyl moiety. The silyl protecting group may then be removed from a compound of the general formula (8) with, for example, an aqueous acid to form an aminoalkyne of the general formula (9). Aminoalkynes of the general formula (9) may be further derivatised, for instance when R_5 is a hydroxyalkyl group, for example, by reacting a compound of the general formula (9) with a silylating agent $(R)_3SiCl$, for example *t*-butyldimethylsilyl chloride, to give a derivative silylated on oxygen of the general formula (9a). In addition, a compound of the general formula (9) may be treated with a base, such as sodium hydride or potassium *bis*(trimethylsilyl)amide followed by a compound R_cL to give a compound of the general formula (9b). In an alternative sequence, a compound of general formula (8) may be treated with a base, such as sodium or potassium *bis*(trimethylsilyl)amide, followed by a compound R_cL, where L represents a halogen or sulphonate ester such as OSO_2Me, or OSO_2-4-tolyl, for example ethyl

iodide, to give, compounds of the general formula (8a), which after removal of the silyl protecting group, gives compounds of the general formula (9b).

Compounds of general formula (8), where R_5 is, for example, 3-chloropropyl can be reacted with a metal cyanide salt, such as sodium cyanide, to give compounds of general formula (8b), which can then be hydrolysed, with for example an aqueous acid, to give the amines of general formula (8c). Compounds of general formula (8), where R_5 is, for example, 3-chloropropyl can be hydrolysed, with for example an aqueous acid, to give amines of general formula (8d).

Scheme 3



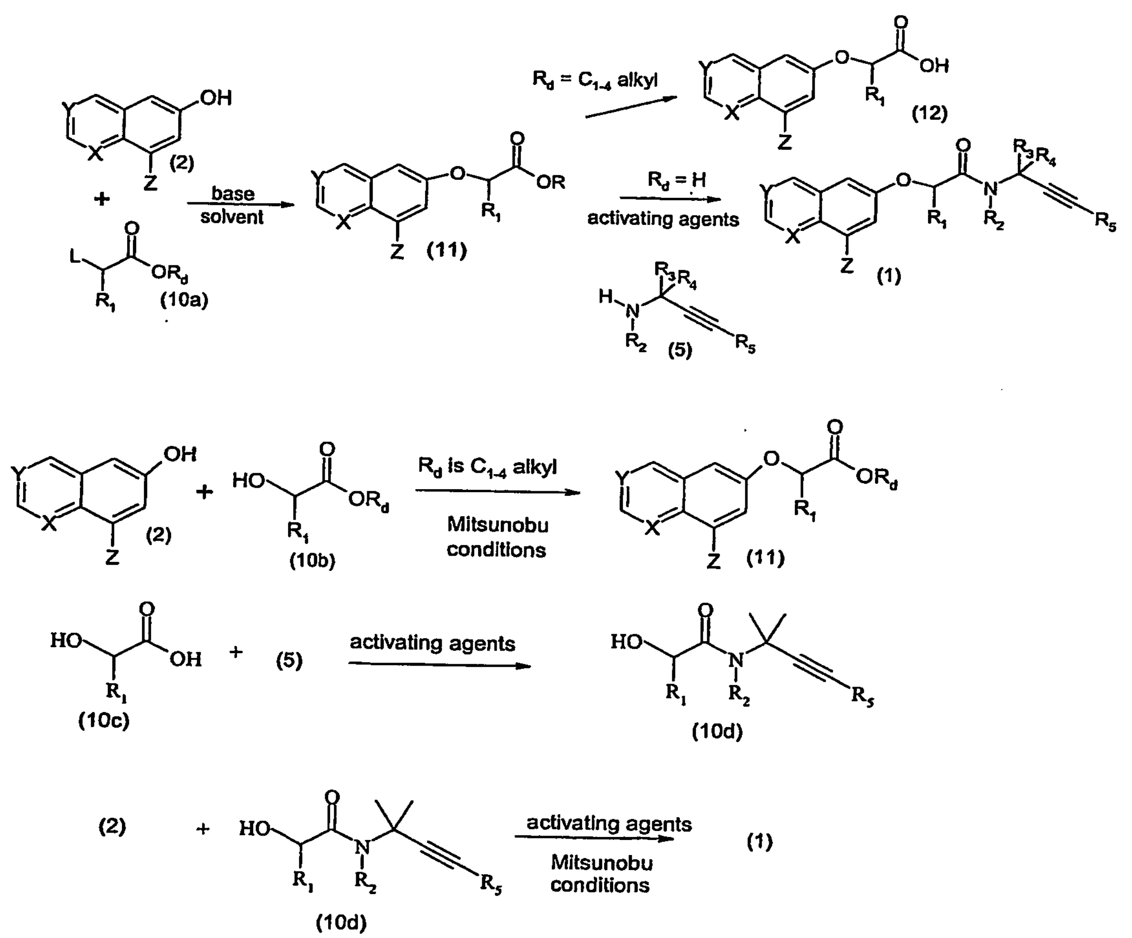
Silyl-protected aminoalkynes of the general formula (7) may be obtained by reacting amines of general formula (6) with 1,2-*bis*-(chlorodimethylsilyl)ethane in the presence of a suitable base, such as a tertiary organic amine base, for example, triethylamine.

Amines of the general formula (6) are either commercially available or may be prepared by standard literature methods (see, for example, EP-A-0834498).

Alternatively, as shown in Scheme 4, compounds of the general formula (1) may be prepared by condensing a compound of the general formula (11), wherein R is H with an amine of the general formula (5) using suitable activating reagents such as 1-hydroxybenzotriazole and *N*-(3-dimethylaminopropyl)-*N*'-ethyl-carbodiimide hydrochloride.

Where R_2 is other than hydrogen, the R_2 group may be introduced into an aminoalkyne of the general formula (9) by known techniques to form an amine of the general formula (5).

<u>Scheme 4</u>



Compounds of the general formula (12) may be prepared by the hydrolysis of the corresponding esters of general formula (11), wherein R_d is C_{1-4} alkyl, using known techniques. The esters of the general formula (11), wherein R_d is C_{1-4} alkyl and also acids

of the general formula (11), wherein R_d is H, may be prepared by reacting a compound of the general formula (2) with an ester or acid of the general formula (10a) in the presence of a suitable base, such as potassium carbonate or sodium hydride, in a suitable solvent, such as *N,N*-dimethylformamide. The esters or acids of the general formula (10a) are either commercially available or may be prepared by standard literature methods from commercially available materials.

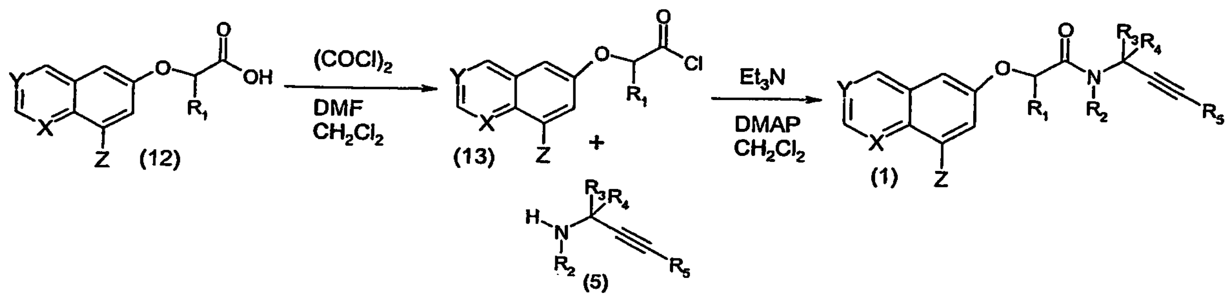
Alternatively, as shown in Scheme 4, compounds of the general formula (11) may be prepared under Mitsunobu conditions by reacting a compound of the general formula (2) with a compound of the general formula (10b), wherein R_d is C_{1-4} alkyl, using a phosphine, such as triphenyl phosphine, and an azoester, such as diethyl azodicarboxylate.

Similarly, compounds of the general formula (1) may be prepared by reacting a compound of general formula (10d) with a compound of the general formula (2) under Mitsunobu conditions using a phosphine, such as triphenyl phosphine, and an azoester, such as diethyl azodicarboxylate. Compounds of general formula (10d) may be prepared from a compound of general formula (10c) and an amine of general formula (5) using suitable activating reagents such as 1-hydroxybenzotriazole and *N*-(3-dimethylamino-propyl)-*N'*-ethyl-carbodiimide hydrochloride. Compounds (10b) and (10c) are either known compounds or may be made from known compounds.

In another method, the compounds of the general formula (1) may be prepared by reacting an acid halide of the general formula (13) with an amine of the general formula (5) in a suitable solvent, such as dichloromethane, in the presence of a tertiary amine, such as triethylamine, and an activating agent, such as 4-dimethylaminopyridine.

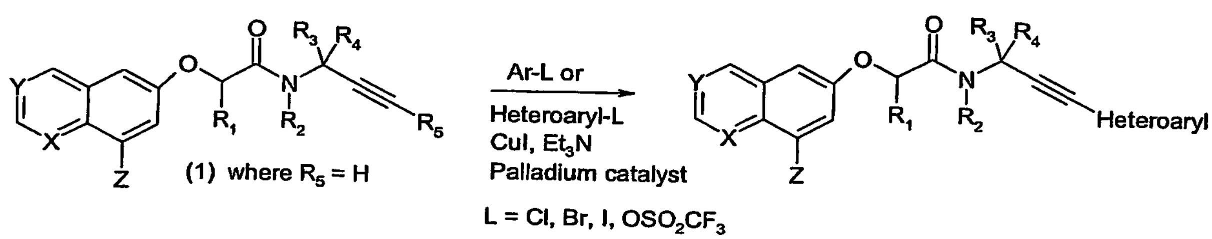
As shown in Scheme 5, an acid halide of the general formula (13) may be prepared by chlorinating a compound of the general formula (12) with a suitable chlorinating agent, such as oxalyl chloride, in a suitable solvent, such as dichloromethane, and in the presence of, for example, *N,N*-dimethylformamide. The compounds of the general formula (12) correspond to the compounds of general formula (11), wherein R is H.

Scheme 5



As shown in Scheme 6, compounds of the general formula (1), wherein R_5 is H, may be reacted under Sonogashira conditions with, for example, optionally substituted phenyl or thienyl chlorides, bromides, iodides or triflates to form substituted phenyl or thienyl compounds of general formula (1), wherein R_5 is an optionally substituted phenyl or thienyl group. A suitable palladium catalyst is tetrakis(triphenylphosphine)-palladium(0).

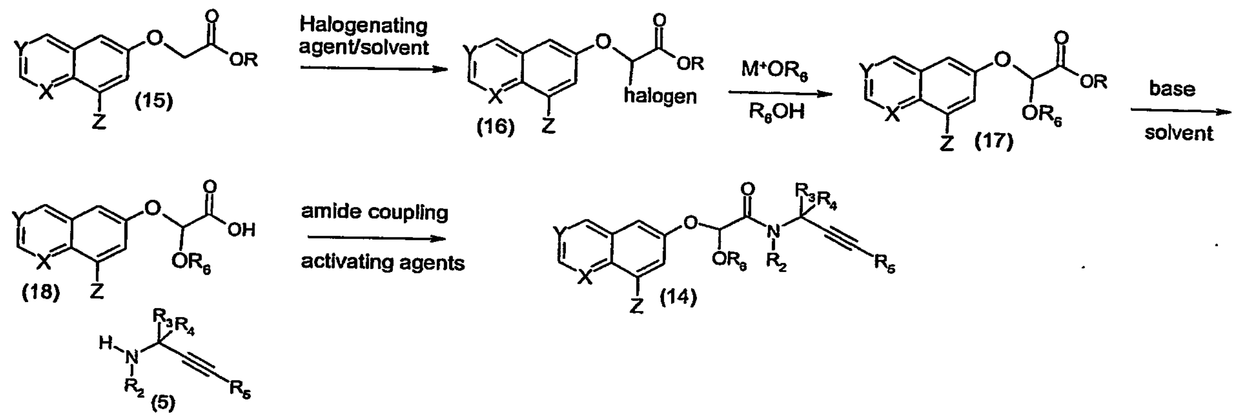
Scheme 6



Compounds of the general formula (1) wherein $R_1$is straight-chain C_{1-4} alkoxy, such as compounds of the general formula (14) wherein R_6 is as defined above, may be prepared as shown in Scheme 7. Thus, esters of the formula (15) may be halogenated to give haloesters of the general formula (16), by treatment with a suitable halogenating agent, such as N-bromosuccinimide, in a suitable solvent such as carbon tetrachloride, at between ambient temperature and the reflux temperature of the solvent. The haloesters of the general formula (16) can be reacted with an alkali metal compound M^+OR_6, where M is suitably sodium or potassium in, for example, an alcohol R_6OH as solvent, at between 0°C and 40°C, preferably at ambient temperature, to give compounds of the general formula (17). The esters (17) can be hydrolysed to acids of the general formula (18), by treatment with an alkali metal hydroxide, such as sodium hydroxide, in an aqueous alcohol R_6OH, at between ambient temperature and reflux.

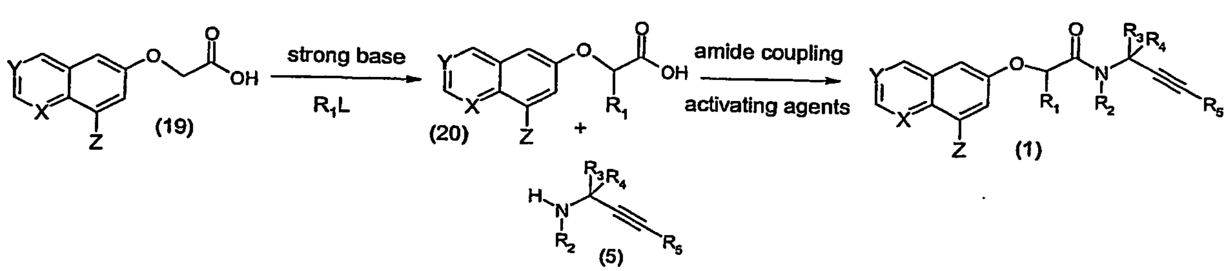
A carboxylic acid of the general formula (18) can be condensed with an amine of the general formula (5) to give a compound of the general formula (14), where R_6 is as defined above, using suitable activating reagents such as 1-hydroxybenzotriazole and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride.

Scheme 7



Compounds of the general formula (1), wherein R_1 is C_{1-4} alkyl, C_{3-4} alkenyl, C_{3-4} alkynyl, or an alkoxyalkyl group where the total number of carbon atoms is 2 or 3, may be prepared as shown in Scheme 8. Thus, the substituted acetic acid (19) may be treated with at least two equivalents of a base, such as lithium di*iso*propylamide, in a suitable solvent such as tetrahydrofuran, at a temperature between –78°C and ambient temperature, with an alkylating agent such as R_1L to give carboxylic acids of the general formula (20) upon acidification.

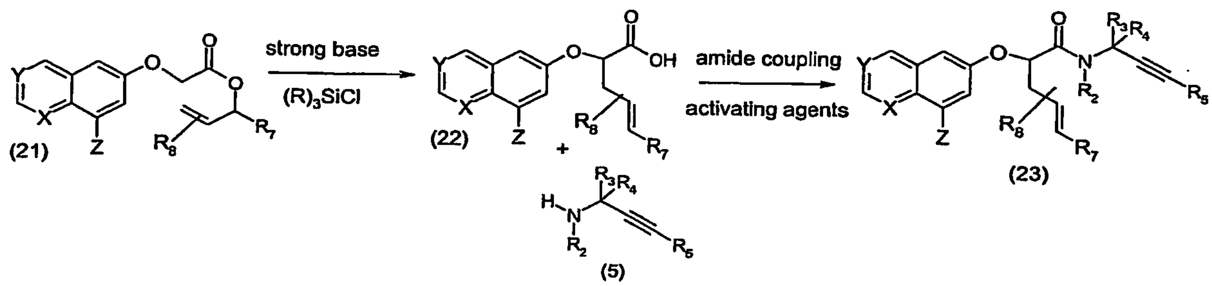
Scheme 8



As shown in Scheme 9, compounds of the general formula (1), where R_1 is a C_{3-6} alkenyl group, may be prepared from esters of the general formula (21), wherein R_7 and R_8 are as defined above. Esters of the general formula (21) are treated with a strong base, such as lithium *bis*(trimethylsilyl)amide, at between –78°C and ambient temperature,

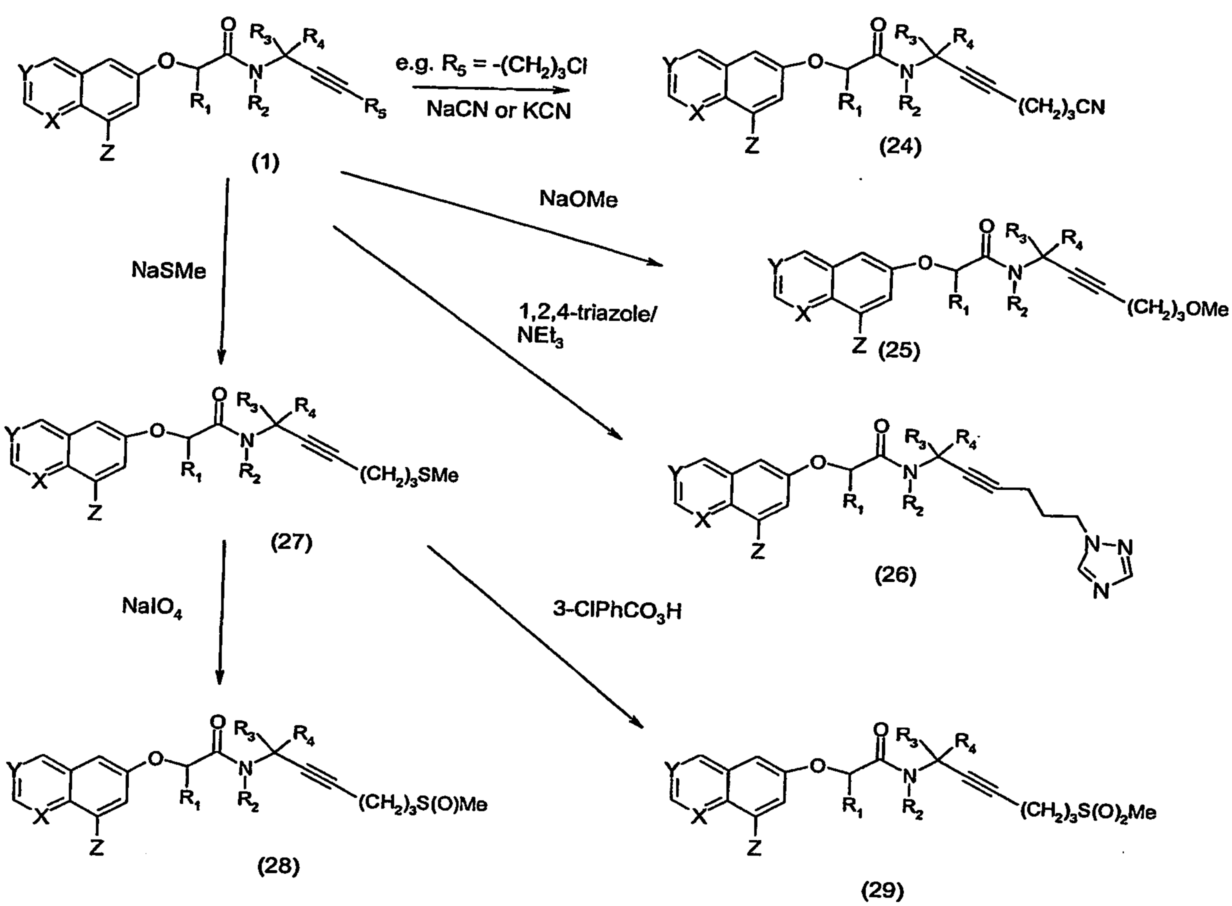
preferably at –78°C, and then reacted with a trialkylsilyl chloride $(R)_3SiCl$, such as trimethylsilyl chloride, or trialkylsilyl triflate $(R)_3SiOSO_2CF_3$, and allowed to warm to ambient temperature. The resultant acids of the general formula (22) obtained after hydrolysis can be condensed with amines of the general formula (5) to give the compounds of the general formula (23), using suitable activating reagents such as 1-hydroxybenzotriazole and *N*-(3-dimethylaminopropyl)-*N'*-ethyl- carbodiimide hydrochloride.

Scheme 9



As shown in Scheme 10, compounds of general formula (1), where R_5 is for example 3-chloropropyl, can be reacted with various nucleophiles such as a metal cyanide salt, for example sodium cyanide, to give compounds of general formula (24), with metal alkoxides, for example sodium methoxide, to give compounds of general formula (25), with 1,2,4-triazole in the presence of base such as triethylamine to give compounds of general formula (26) and with metal thioalkoxides, for example sodium methanethiolate, to give compounds of general formula (27). Compounds of general formula (27) can be treated with oxidising agents such as sodium periodate, to give sulphoxides of general formula (28), or with oxidising agents such as 3-chloroperbenzoic acid, to give sulphones of general formula (29).

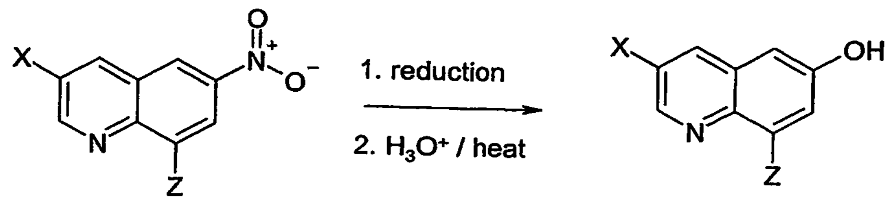
Scheme 10



Methods for the preparation of optionally substituted hydroxyquinolines or substituted quinolines suitable for transformation to optionally substituted hydroxy-quinolines may be found in the literature, e.g. The Chemistry of Heterocyclic Compounds, Ed. G. Jones, John Wiley, Interscience, London and references cited therein.

For example, as shown in Scheme 11, 6-nitroquinolines optionally substituted in the 3 or 8 or 3 and 8 positions may be reduced to the corresponding optionally substituted 6-aminoquinolines. These aminoquinolines may then be hydrolysed, for example using a strong aqueous acid such as sulphuric, phosphoric or hydrochloric acid, to the corresponding optionally substituted 6-hydroxyquinolines.

Scheme 11



e.g. X = H, halo
Z = H, halo, alkyl, alkoxy, etc.

Methods for the preparation of optionally substituted hydroxyquinazolines or substituted quinazolines suitable for transformation to substituted hydroxyquinazolines may be found in the literature, e.g. The Chemistry of Heterocyclic Compounds, Ed. D. J. Brown, John Wiley, Interscience, London and references cited therein.

Other compounds of the invention may be prepared by transforming the substituents in the compounds of the general formula (1) using known procedures e.g. by the alkylation of compounds of the general formula (1), wherein R_2 is H or R_5 is H.

The compounds of formula (1) are active fungicides and may be used to control one or more of the following pathogens: *Pyricularia oryzae* (*Magnaporthe grisea*) on rice and wheat and other *Pyricularia* spp. on other hosts; *Puccinia triticina* (or *recondita*), *Puccinia striiformis* and other rusts on wheat, *Puccinia hordei*, *Puccinia striiformis* and other rusts on barley, and rusts on other hosts (for example turf, rye, coffee, pears, apples, peanuts, sugar beet, vegetables and ornamental plants); *Erysiphe cichoracearum* on cucurbits (for example melon); *Blumeria* (or *Erysiphe*) *graminis* (powdery mildew) on barley, wheat, rye and turf and other powdery mildews on various hosts, such as *Sphaerotheca macularis* on hops, *Sphaerotheca fusca (Sphaerotheca fuliginea)* on cucurbits (for example cucumber), *Leveillula taurica* on tomatoes, aubergine and green pepper, *Podosphaera leucotricha* on apples and *Uncinula necator* on vines; *Cochliobolus* spp., *Helminthosporium* spp., *Drechslera* spp. (*Pyrenophora* spp.), *Rhynchosporium* spp., *Mycosphaerella graminicola* (*Septoria tritici)* and *Phaeosphaeria nodorum* (*Stagonospora nodorum* or *Septoria nodorum*), *Pseudocercosporella herpotrichoides* and *Gaeumannomyces graminis* on cereals (for example wheat, barley, rye), turf and other hosts; *Cercospora arachidicola* and *Cercosporidium personatum* on peanuts and other *Cercospora* spp. on other hosts, for example sugar beet, bananas, soya beans and rice; *Botrytis cinerea* (grey mould) on tomatoes, strawberries, vegetables, vines and other hosts

and other *Botrytis* spp. on other hosts; *Alternaria* spp. on vegetables (for example carrots), oil-seed rape, apples, tomatoes, potatoes, cereals (for example wheat) and other hosts; *Venturia* spp. (including *Venturia inaequalis* (scab)) on apples, pears, stone fruit, tree nuts and other hosts; *Cladosporium* spp. on a range of hosts including cereals (for example wheat) and tomatoes; *Monilinia* spp. on stone fruit, tree nuts and other hosts; *Didymella* spp. on tomatoes, turf, wheat, cucurbits and other hosts; *Phoma* spp. on oil-seed rape, turf, rice, potatoes, wheat and other hosts; *Aspergillus* spp. and *Aureobasidium* spp. on wheat, lumber and other hosts; *Ascochyta* spp. on peas, wheat, barley and other hosts; *Stemphylium* spp. (*Pleospora* spp.) on apples, pears, onions and other hosts; summer diseases (for example bitter rot (*Glomerella cingulata*), black rot or frogeye leaf spot (*Botryosphaeria obtusa*), Brooks fruit spot (*Mycosphaerella pomi*), Cedar apple rust (*Gymnosporangium juniperi-virginianae*), sooty blotch (*Gloeodes pomigena*), flyspeck (*Schizothyrium pomi*) and white rot (*Botryosphaeria dothidea*)) on apples and pears; *Plasmopara viticola* on vines; other downy mildews, such as *Bremia lactucae* on lettuce, *Peronospora* spp. on soybeans, tobacco, onions and other hosts, *Pseudoperonospora humuli* on hops and *Pseudoperonospora cubensis* on cucurbits; *Pythium* spp. (including *Pythium ultimum*) on turf and other hosts; *Phytophthora infestans* on potatoes and tomatoes and other *Phytophthora* spp. on vegetables, strawberries, avocado, pepper, ornamentals, tobacco, cocoa and other hosts; *Thanatephorus cucumeris* on rice and turf and other *Rhizoctonia* spp. on various hosts such as wheat and barley, peanuts, vegetables, cotton and turf; *Sclerotinia* spp. on turf, peanuts, potatoes, oil-seed rape and other hosts; *Sclerotium* spp. on turf, peanuts and other hosts; *Gibberella fujikuroi* on rice; *Colletotrichum* spp. on a range of hosts including turf, coffee and vegetables; *Laetisaria fuciformis* on turf; *Mycosphaerella* spp. on bananas, peanuts, citrus, pecans, papaya and other hosts; *Diaporthe* spp. on citrus, soybean, melon, pears, lupin and other hosts; *Elsinoe* spp. on citrus, vines, olives, pecans, roses and other hosts; *Verticillium* spp. on a range of hosts including hops, potatoes and tomatoes; *Pyrenopeziza* spp. on oil-seed rape and other hosts; *Oncobasidium theobromae* on cocoa causing vascular streak dieback; *Fusarium* spp., *Typhula* spp., *Microdochium nivale*, *Ustilago* spp., *Urocystis* spp., *Tilletia* spp. and *Claviceps purpurea* on a variety of hosts but particularly wheat, barley, turf and maize; *Ramularia* spp. on sugar beet, barley and other hosts; post-harvest diseases particularly of fruit (for example *Penicillium digitatum*,

Penicillium italicum and *Trichoderma viride* on oranges, *Colletotrichum musae* and *Gloeosporium musarum* on bananas and *Botrytis cinerea* on grapes); other pathogens on vines, notably *Eutypa lata, Guignardia bidwellii, Phellinus igniarus, Phomopsis viticola, Pseudopeziza tracheiphila* and *Stereum hirsutum*; other pathogens on trees (for example *Lophodermium seditiosum*) or lumber, notably *Cephaloascus fragrans, Ceratocystis* spp., *Ophiostoma piceae, Penicillium* spp., *Trichoderma pseudokoningii, Trichoderma viride, Trichoderma harzianum, Aspergillus niger, Leptographium lindbergi* and *Aureobasidium pullulans*; and fungal vectors of viral diseases (for example *Polymyxa graminis* on cereals as the vector of barley yellow mosaic virus (BYMV) and *Polymyxa betae* on sugar beet as the vector of rhizomania).

The compounds of formula (I) show particularly good activity against the Oomycete class of pathogens such as *Phytophthora infestans, Plasmopara* species, e.g.*Plasmopara viticola* and *Pythium* species e.g. *Pythium ultimum.*

A compound of formula (1) may move acropetally, basipetally or locally in plant tissue to be active against one or more fungi. Moreover, a compound of formula (1) may be volatile enough to be active in the vapour phase against one or more fungi on the plant.

The invention therefore provides a method of combating or controlling phytopathogenic fungi which comprises applying a fungicidally effective amount of a compound of formula (1), or a composition containing a compound of formula (1), to a plant, to a seed of a plant, to the locus of the plant or seed or to soil or any other plant growth medium, e.g. nutrient solution.

The term "plant" as used herein includes seedlings, bushes and trees. Furthermore, the fungicidal method of the invention includes protectant, curative, systemic, eradicant and antisporulant treatments.

The compounds of formula (1) are preferably used for agricultural, horticultural and turfgrass purposes in the form of a composition.

In order to apply a compound of formula (1) to a plant, to a seed of a plant, to the locus of the plant or seed or to soil or any other growth medium, a compound of formula (1) is usually formulated into a composition which includes, in addition to the compound of formula (1), a suitable inert diluent or carrier and, optionally, a surface active agent (SFA). SFAs are chemicals which are able to modify the properties of an interface (for example, liquid/solid, liquid/air or liquid/liquid interfaces) by lowering the interfacial

tension and thereby leading to changes in other properties (for example dispersion, emulsification and wetting). It is preferred that all compositions (both solid and liquid formulations) comprise, by weight, 0.0001 to 95%, more preferably 1 to 85%, for example 5 to 60%, of a compound of formula (1). The composition is generally used for the control of fungi such that a compound of formula (1) is applied at a rate of from 0.1g to10kg per hectare, preferably from 1g to 6kg per hectare, more preferably from 1g to 1kg per hectare.

When used in a seed dressing, a compound of formula (1) is used at a rate of 0.0001g to 10g (for example 0.001g or 0.05g), preferably 0.005g to 10g, more preferably 0.005g to 4g, per kilogram of seed.

In another aspect the present invention provides a fungicidal composition comprising a fungicidally effective amount of a compound of formula (1) and a suitable carrier or diluent therefor.

In a still further aspect the invention provides a method of combating and controlling fungi at a locus, which comprises treating the fungi, or the locus of the fungi with a fungicidally effective amount of a composition comprising a compound of formula (1).

The compositions can be chosen from a number of formulation types, including dustable powders (DP), soluble powders (SP), water soluble granules (SG), water dispersible granules (WG), wettable powders (WP), granules (GR) (slow or fast release), soluble concentrates (SL), oil miscible liquids (OL), ultra low volume liquids (UL), emulsifiable concentrates (EC), dispersible concentrates (DC), emulsions (both oil in water (EW) and water in oil (EO)), micro-emulsions (ME), suspension concentrates (SC), aerosols, fogging/smoke formulations, capsule suspensions (CS) and seed treatment formulations. The formulation type chosen in any instance will depend upon the particular purpose envisaged and the physical, chemical and biological properties of the compound of formula (1).

Dustable powders (DP) may be prepared by mixing a compound of formula (1) with one or more solid diluents (for example natural clays, kaolin, pyrophyllite, bentonite, alumina, montmorillonite, kieselguhr, chalk, diatomaceous earths, calcium phosphates, calcium and magnesium carbonates, sulphur, lime, flours, talc and other

organic and inorganic solid carriers) and mechanically grinding the mixture to a fine powder.

Soluble powders (SP) may be prepared by mixing a compound of formula (1) with one or more water-soluble inorganic salts (such as sodium bicarbonate, sodium carbonate or magnesium sulphate) or one or more water-soluble organic solids (such as a polysaccharide) and, optionally, one or more wetting agents, one or more dispersing agents or a mixture of said agents to improve water dispersibility/solubility. The mixture is then ground to a fine powder. Similar compositions may also be granulated to form water soluble granules (SG).

Wettable powders (WP) may be prepared by mixing a compound of formula (1) with one or more solid diluents or carriers, one or more wetting agents and, preferably, one or more dispersing agents and, optionally, one or more suspending agents to facilitate the dispersion in liquids. The mixture is then ground to a fine powder. Similar compositions may also be granulated to form water dispersible granules (WG).

Granules (GR) may be formed either by granulating a mixture of a compound of formula (1) and one or more powdered solid diluents or carriers, or from pre-formed blank granules by absorbing a compound of formula (1) (or a solution thereof, in a suitable agent) in a porous granular material (such as pumice, attapulgite clays, fuller's earth, kieselguhr, diatomaceous earths or ground corn cobs) or by adsorbing a compound of formula (1) (or a solution thereof, in a suitable agent) on to a hard core material (such as sands, silicates, mineral carbonates, sulphates or phosphates) and drying if necessary. Agents which are commonly used to aid absorption or adsorption include solvents (such as aliphatic and aromatic petroleum solvents, alcohols, ethers, ketones and esters) and sticking agents (such as polyvinyl acetates, polyvinyl alcohols, dextrins, sugars and vegetable oils). One or more other additives may also be included in granules (for example an emulsifying agent, wetting agent or dispersing agent).

Dispersible Concentrates (DC) may be prepared by dissolving a compound of formula (1) in water or an organic solvent, such as a ketone, alcohol or glycol ether. These solutions may contain a surface active agent (for example to improve water dilution or prevent crystallisation in a spray tank).

Emulsifiable concentrates (EC) or oil-in-water emulsions (EW) may be prepared by dissolving a compound of formula (1) in an organic solvent (optionally containing one

or more wetting agents, one or more emulsifying agents or a mixture of said agents). Suitable organic solvents for use in ECs include aromatic hydrocarbons (such as alkylbenzenes or alkylnaphthalenes, exemplified by SOLVESSO 100, SOLVESSO 150 and SOLVESSO 200; SOLVESSO is a Registered Trade Mark), ketones (such as cyclohexanone or methylcyclohexanone), alcohols (such as benzyl alcohol, furfuryl alcohol or butanol), *N*-alkylpyrrolidones (such as *N*-methylpyrrolidone or *N*-octylpyrrolidone), dimethyl amides of fatty acids (such as C_8-C_{10} fatty acid dimethylamide) and chlorinated hydrocarbons. An EC product may spontaneously emulsify on addition to water, to produce an emulsion with sufficient stability to allow spray application through appropriate equipment. Preparation of an EW involves obtaining a compound of formula (1) either as a liquid (if it is not a liquid at room temperature, it may be melted at a reasonable temperature, typically below 70°C) or in solution (by dissolving it in an appropriate solvent) and then emulsifying the resultant liquid or solution into water containing one or more SFAs, under high shear, to produce an emulsion. Suitable solvents for use in EWs include vegetable oils, chlorinated hydrocarbons (such as chlorobenzenes), aromatic solvents (such as alkylbenzenes or alkylnaphthalenes) and other appropriate organic solvents which have a low solubility in water.

Microemulsions (ME) may be prepared by mixing water with a blend of one or more solvents with one or more SFAs, to produce spontaneously a thermodynamically stable isotropic liquid formulation. A compound of formula (1) is present initially in either the water or the solvent/SFA blend. Suitable solvents for use in MEs include those hereinbefore described for use in in ECs or in EWs. An ME may be either an oil-in-water or a water-in-oil system (which system is present may be determined by conductivity measurements) and may be suitable for mixing water-soluble and oil-soluble pesticides in the same formulation. An ME is suitable for dilution into water, either remaining as a microemulsion or forming a conventional oil-in-water emulsion.

Suspension concentrates (SC) may comprise aqueous or non-aqueous suspensions of finely divided insoluble solid particles of a compound of formula (1). SCs may be prepared by ball or bead milling the solid compound of formula (1) in a suitable medium, optionally with one or more dispersing agents, to produce a fine particle suspension of the compound. One or more wetting agents may be included in the composition and a

suspending agent may be included to reduce the rate at which the particles settle. Alternatively, a compound of formula (1) may be dry milled and added to water, containing agents hereinbefore described, to produce the desired end product.

Aerosol formulations comprise a compound of formula (1) and a suitable propellant (for example *n*-butane). A compound of formula (1) may also be dissolved or dispersed in a suitable medium (for example water or a water miscible liquid, such as *n*-propanol) to provide compositions for use in non-pressurised, hand-actuated spray pumps.

A compound of formula (1) may be mixed in the dry state with a pyrotechnic mixture to form a composition suitable for generating, in an enclosed space, a smoke containing the compound.

Capsule suspensions (CS) may be prepared in a manner similar to the preparation of EW formulations but with an additional polymerisation stage such that an aqueous dispersion of oil droplets is obtained, in which each oil droplet is encapsulated by a polymeric shell and contains a compound of formula (1) and, optionally, a carrier or diluent therefor. The polymeric shell may be produced by either an interfacial polycondensation reaction or by a coacervation procedure. The compositions may provide for controlled release of the compound of formula (1) and they may be used for seed treatment. A compound of formula (1) may also be formulated in a biodegradable polymeric matrix to provide a slow, controlled release of the compound.

A composition may include one or more additives to improve the biological performance of the composition (for example by improving wetting, retention or distribution on surfaces; resistance to rain on treated surfaces; or uptake or mobility of a compound of formula (1)). Such additives include surface active agents, spray additives based on oils, for example certain mineral oils or natural plant oils (such as soy bean and rape seed oil), and blends of these with other bio-enhancing adjuvants (ingredients which may aid or modify the action of a compound of formula (1)).

A compound of formula (1) may also be formulated for use as a seed treatment, for example as a powder composition, including a powder for dry seed treatment (DS), a water soluble powder (SS) or a water dispersible powder for slurry treatment (WS), or as a liquid composition, including a flowable concentrate (FS), a solution (LS) or a capsule suspension (CS). The preparations of DS, SS, WS, FS and LS compositions are very

similar to those of, respectively, DP, SP, WP, SC and DC compositions described above. Compositions for treating seed may include an agent for assisting the adhesion of the composition to the seed (for example a mineral oil or a film-forming barrier).

Wetting agents, dispersing agents and emulsifying agents may be SFAs of the cationic, anionic, amphoteric or non-ionic type.

Suitable SFAs of the cationic type include quaternary ammonium compounds (for example cetyltrimethyl ammonium bromide), imidazolines and amine salts.

Suitable anionic SFAs include alkali metals salts of fatty acids, salts of aliphatic monoesters of sulphuric acid (for example sodium lauryl sulphate), salts of sulphonated aromatic compounds (for example sodium dodecylbenzenesulphonate, calcium dodecylbenzenesulphonate, butylnaphthalene sulphonate and mixtures of sodium di-*iso*propyl- and tri-*iso*propyl-naphthalene sulphonates), ether sulphates, alcohol ether sulphates (for example sodium laureth-3-sulphate), ether carboxylates (for example sodium laureth-3-carboxylate), phosphate esters (products from the reaction between one or more fatty alcohols and phosphoric acid (predominately mono-esters) or phosphorus pentoxide (predominately di-esters), for example the reaction between lauryl alcohol and tetraphosphoric acid; additionally these products may be ethoxylated), sulphosuccinamates, paraffin or olefine sulphonates, taurates and lignosulphonates.

Suitable SFAs of the amphoteric type include betaines, propionates and glycinates.

Suitable SFAs of the non-ionic type include condensation products of alkylene oxides, such as ethylene oxide, propylene oxide, butylene oxide or mixtures thereof, with fatty alcohols (such as oleyl alcohol or cetyl alcohol) or with alkylphenols (such as octylphenol, nonylphenol or octylcresol); partial esters derived from long chain fatty acids or hexitol anhydrides; condensation products of said partial esters with ethylene oxide; block polymers (comprising ethylene oxide and propylene oxide); alkanolamides; simple esters (for example fatty acid polyethylene glycol esters); amine oxides (for example lauryl dimethyl amine oxide); and lecithins.

Suitable suspending agents include hydrophilic colloids (such as polysaccharides, polyvinylpyrrolidone or sodium carboxymethylcellulose) and swelling clays (such as bentonite or attapulgite).

A compound of formula (1) may be applied by any of the known means of applying fungicidal compounds. For example, it may be applied, formulated or unformulated, to any part of the plant, including the foliage, stems, branches or roots, to the seed before it is planted or to other media in which plants are growing or are to be planted (such as soil surrounding the roots, the soil generally, paddy water or hydroponic culture systems), directly or it may be sprayed on, dusted on, applied by dipping, applied as a cream or paste formulation, applied as a vapour or applied through distribution or incorporation of a composition (such as a granular composition or a composition packed in a water-soluble bag) in soil or an aqueous environment.

A compound of formula (1) may also be injected into plants or sprayed onto vegetation using electrodynamic spraying techniques or other low volume methods, or applied by land or aerial irrigation systems.

Compositions for use as aqueous preparations (aqueous solutions or dispersions) are generally supplied in the form of a concentrate containing a high proportion of the active ingredient, the concentrate being added to water before use. These concentrates, which may include DCs, SCs, ECs, EWs, MEs SGs, SPs, WPs, WGs and CSs, are often required to withstand storage for prolonged periods and, after such storage, to be capable of addition to water to form aqueous preparations which remain homogeneous for a sufficient time to enable them to be applied by conventional spray equipment. Such aqueous preparations may contain varying amounts of a compound of formula (1) (for example 0.0001 to 10%, by weight) depending upon the purpose for which they are to be used.

A compound of formula (1) may be used in mixtures with fertilisers (for example nitrogen-, potassium- or phosphorus-containing fertilisers). Suitable formulation types include granules of fertiliser. The mixtures suitably contain up to 25% by weight of the compound of formula (1).

The invention therefore also provides a fertiliser composition comprising a fertiliser and a compound of formula (1).

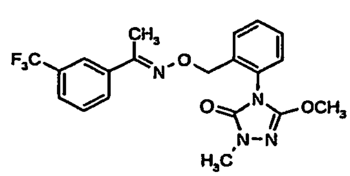
The compositions of this invention may contain other compounds having biological activity, for example micronutrients or compounds having similar or complementary fungicidal activity or which possess plant growth regulating, herbicidal, insecticidal, nematicidal or acaricidal activity.

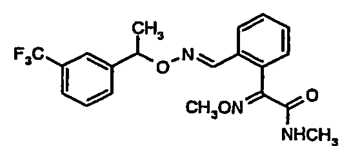
By including another fungicide, the resulting composition may have a broader spectrum of activity or a greater level of intrinsic activity than the compound of formula (1) alone. Further the other fungicide may have a synergistic effect on the fungicidal activity of the compound of formula (1).

The compound of formula (1) may be the sole active ingredient of the composition or it may be admixed with one or more additional active ingredients such as a pesticide, fungicide, synergist, herbicide or plant growth regulator where appropriate. An additional active ingredient may: provide a composition having a broader spectrum of activity or increased persistence at a locus; synergise the activity or complement the activity (for example by increasing the speed of effect or overcoming repellency) of the compound of formula (1); or help to overcome or prevent the development of resistance to individual components. The particular additional active ingredient will depend upon the intended utility of the composition.

Examples of fungicidal compounds which may be included in the composition of the invention are AC 382042 (*N*-(1-cyano-1,2-dimethylpropyl)-2-(2,4-dichlorophenoxy) propionamide), acibenzolar-S-methyl, alanycarb, aldimorph, anilazine, azaconazole, azafenidin, azoxystrobin, benalaxyl, benomyl, benthiavalicarb, biloxazol, bitertanol, blasticidin S, boscalid (new name for nicobifen), bromuconazole, bupirimate, captafol, captan, carbendazim, carbendazim chlorhydrate, carboxin, carpropamid, carvone, CGA 41396, CGA 41397, chinomethionate, chlorbenzthiazone, chlorothalonil, chlorozolinate, clozylacon, copper containing compounds such as copper oxychloride, copper oxyquinolate, copper sulphate, copper tallate, and Bordeaux mixture, cyamidazosulfamid, cyazofamid (IKF-916), cyflufenamid, cymoxanil, cyproconazole, cyprodinil, debacarb, di-2-pyridyl disulphide 1,1'-dioxide, dichlofluanid, diclocymet, diclomezine, dicloran, diethofencarb, difenoconazole, difenzoquat, diflumetorim, *O,O*-di-*iso*-propyl-*S*-benzyl thiophosphate, dimefluazole, dimetconazole, dimethirimol, dimethomorph, dimoxystrobin, diniconazole, dinocap, dithianon, dodecyl dimethyl ammonium chloride, dodemorph, dodine, doguadine, edifenphos, epoxiconazole, ethaboxam, ethirimol, ethyl (*Z*)-*N*-benzyl-*N*([methyl(methyl-thioethylideneaminooxycarbonyl)amino]thio)-β-alaninate, etridiazole, famoxadone, fenamidone, fenarimol, fenbuconazole, fenfuram, fenhexamid, fenoxanil (AC 382042), fenpiclonil, fenpropidin, fenpropimorph, fentin acetate, fentin hydroxide, ferbam, ferimzone, fluazinam, fludioxonil, flumetover,

flumorph, fluoroimide, fluoxastrobin, fluquinconazole, flusilazole, flusulfamide, flutolanil, flutriafol, folpet, fosetyl-aluminium, fuberidazole, furalaxyl, furametpyr, guazatine, hexaconazole, hydroxyisoxazole, hymexazole, imazalil, imibenconazole, iminoctadine, iminoctadine triacetate, ipconazole, iprobenfos, iprodione, iprovalicarb, isopropanyl butyl carbamate, isoprothiolane, kasugamycin, kresoxim-methyl, LY186054, LY211795, LY 248908, mancozeb, maneb, mefenoxam, mepanipyrim, mepronil, metalaxyl, metalaxyl M, metconazole, metiram, metiram-zinc, metominostrobin, metrafenone, MON65500 (*N*-allyl-4,5-dimethyl-2-trimethylsilylthiophene-3-carboxamide), myclobutanil, NTN0301, neoasozin, nickel dimethyldithiocarbamate, nitrothale-isopropyl, nuarimol, ofurace, organomercury compounds, orysastrobin, oxadixyl, oxasulfuron, oxolinic acid, oxpoconazole, oxycarboxin, pefurazoate, penconazole, pencycuron, phenazin oxide, phosphorus acids, phthalide, picoxystrobin, polyoxin D, polyram, probenazole, prochloraz, procymidone, propamocarb, propamocarb hydrochloride, propiconazole, propineb, propionic acid, proquinazid, prothioconazole, pyraclostrobin, pyrazophos, pyrifenox, pyrimethanil, pyroquilon, pyroxyfur, pyrrolnitrin, quaternary ammonium compounds, quinomethionate, quinoxyfen, quintozene, silthiofam (MON 65500), S-imazalil, simeconazole, sipconazole, sodium pentachlorophenate, spiroxamine, streptomycin, sulphur, tebuconazole, tecloftalam, tecnazene, tetraconazole, thiabendazole, thifluzamide, 2-(thiocyanomethylthio)benzothiazole, thiophanate-methyl, thiram, tiadinil, timibenconazole, tolclofos-methyl, tolylfluanid, triadimefon, triadimenol, triazbutil, triazoxide, tricyclazole, tridemorph, trifloxystrobin, triflumizole, triforine, triticonazole, validamycin A, vapam, vinclozolin, XRD-563, zineb, ziram, zoxamide and compounds of the formulae:





The compounds of formula (1) may be mixed with soil, peat or other rooting media for the protection of plants against seed-borne, soil-borne or foliar fungal diseases.

Some mixtures may comprise active ingredients which have significantly different physical, chemical or biological properties such that they do not easily lend themselves to

the same conventional formulation type. In these circumstances other formulation types may be prepared. For example, where one active ingredient is a water insoluble solid and the other a water insoluble liquid, it may nevertheless be possible to disperse each active ingredient in the same continuous aqueous phase by dispersing the solid active ingredient as a suspension (using a preparation analogous to that of an SC) but dispersing the liquid active ingredient as an emulsion (using a preparation analogous to that of an EW). The resultant composition is a suspoemulsion (SE) formulation.

The invention is illustrated by the following Examples in which the following abbreviations are used:

ml = millilitres
g = grammes
ppm = parts per million
M^+ = mass ion
s = singlet
d = doublet
br s = broad singlet
t = triplet
DMSO = dimethylsulphoxide
NMR = nuclear magnetic resonance
HPLC = high performance liquid chromatography
q = quartet
m = multiplet
ppm = parts per million
m.p. = melting point

EXAMPLE 1

This Example illustrates the preparation of 2-(6-quinolinyloxy)-*N*-(4-methylpent-2-yn-4-yl) butyramide (Compound No. 2 of Table 1)

<u>Stage 1: Preparation of 2-bromo-*N*-(4-methylpent-2-yn-4-yl) butyramide</u>

<u>Step 1: Preparation of 4-amino-4-methylpent-2-yne hydrochloride</u>

3-Amino-3-methylbutyne (commercially available as 90% aqueous solution; 16.6g) was dissolved in dichloromethane (150ml), dried over sodium sulphate and filtered to give a solution containing 14.9g of amine. To the stirred solution of amine under an atmosphere of nitrogen at ambient temperature was added dry triethylamine (48.4ml). 1,2-*Bis*-(chlorodimethylsilyl)ethane (38.98g) in dichloromethane (100ml) was then added dropwise, maintaining the reaction temperature at 15°C by cooling. The mixture was stirred for 3 hours, the colourless solid, which had formed during the reaction, was filtered from solution and the filtrate was evaporated under reduced pressure to give a paste. The paste was extracted into hexane and refiltered. The filtrate was evaporated under reduced pressure and the oil obtained was distilled to give 1-(1,1-

dimethyl-2-propynyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane, 21.5g, b.p. 41°C at 0.06 mm Hg pressure.

^{1}H NMR ($CDCl_3$) δ: 0.16(12H, s); 0.60(4H,s); 1.48(6H, s); 2.24(1H, s).

Step 2

The product from Step 1 (13.0g) in dry tetrahydrofuran (140ml) was cooled to -70°C under an atmosphere of nitrogen with stirring and a solution of *n*-butyl lithium (23.1ml of 2.5M solution in hexanes) was added at –65 to -70°C during 5minutes. The mixture was allowed to warm to -5°C and methyl iodide (3.93ml) was added dropwise over 10 minutes. The reaction mixture was allowed to warm to 10°C when an exothermic reaction occurred. The mixture was maintained at 20°C by cooling for 2 hours then evaporated under reduced pressure to a small volume. The residue was dissolved in hexane, filtered to remove the insoluble material and evaporated under reduced pressure to give 1-(1,1-dimethyl-2-butynyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane as a yellow oil, 13.0g.

^{1}H NMR ($CDCl_3$) δ: 0.10(12H,s); 0.56(4H, s); 1.40(6H, s); 1.72(3H, s).

Step 3

The product from Step 2 (13.0g) was added slowly to aqueous hydrochloric acid (35ml, 4M) at 0°C with stirring. The emulsion formed was stirred for 0.5 hours then taken to pH14 with aqueous sodium hydroxide (4M) while maintaining the reaction mixture at 0°C by cooling in ice. The aqueous mixture was extracted into dichloromethane (three times) and the extracts combined, dried over sodium sulphate and filtered. The filtrate was made acidic by adding an excess of a saturated solution of hydrogen chloride in 1,4-dioxan. The mixture was concentrated under reduced pressure until a colourless precipitate was formed. Hexane was added to the suspension and the solid was filtered from solution. The solid was washed with dry diethyl ether and placed under vacuum to remove any residual solvents to give the required product as a colourless solid, 5.0g.

^{1}H NMR (d_6-DMSO) δ: 1.74(6H, s); 1.82(3H, s); 8.74(3H, br s).

Step 4: The preparation of 2-bromo-*N*-(4-methylpent-2-yn-4-yl) butyramide

The product from Step3 (5.0g) was dissolved in dry dichloromethane (200ml), cooled to 3°C with stirring then 2-bromobutyryl bromide (6.25g) was added followed by dropwise addition of dry triethylamine (10.93ml), maintaining the reaction at 5°C. The

suspension, which had formed during the reaction, was stirred at ambient temperature for 1hour then water was added. The organic phase was separated, washed with water, dried over magnesium sulphate then evaporated under reduced pressure. The residue was fractionated by chromatography (silica; hexane / diethyl ether, 3:1 by volume) to give the required product, 5.2g, as a colourless solid, m.p. 79-81°C.

^{1}H NMR ($CDCl_3$) δ: 1.04(3H, t); 1.64(6H, s); 1.84(3H, s); 2.04-2.18(2H, m); 4.20-4.24(1H, m); 6.46(1H, br s).

Stage 2

6-Hydroxyquinoline (0.46g) in dry *N,N*-dimethylformamide (10ml) was added dropwise to a stirred suspension of sodium hydride (0.10g, 80% dispersion in mineral oil) in dry *N,N*-dimethylformamide under an atmosphere of nitrogen at ambient temperature. The green solution was stirred at ambient temperature for 1hour and a solution of 2-bromo-*N*-(4-methylpent-2-yn-4-yl) butyramide (0.74g) in dry *N,N*-dimethylformamide (10ml) was added. The mixture was stirred at ambient temperature for 18 hours, poured into water and extracted into diethyl ether (three times). The organic extracts were combined, washed with dilute aqueous sodium hydroxide, water (twice), dried over magnesium sulphate and evaporated under reduced pressure to give a gum. The gum was fractionated by chromatography (silica; diethyl ether) to give the required product, 0.44g, as a colourless gum.

^{1}H NMR (CDCl3) δ: 1.06-1.10(3H, t); 1.56-1.60(6H, d); 1.76(3H, s); 1.98-2.10(2H, m); 4.54-4.58(1H, m); 6.42(1H, s); 7.10(1H, m); 7.36-7.44(2H, m); 8.02-8.06(2H, m); 8.82(1H, d).

EXAMPLE 2

This Example illustrates the preparation of 2-(6-quinolinyloxy)-*N*-(1-*tert*-butyldimethylsilyloxy-4-methylpent-2-yn-4-yl)butyramide (Compound No. 50 of Table 1)

Stage 1: Preparation of 4-amino-1-hydroxy-4-methylpent-2-yne hydrochloride.

Step 1

1-(1,1-Dimethyl-2-propynyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane (22.6g) in dry tetrahydrofuran (250ml) was cooled to –50°C under an atmosphere of nitrogen with stirring and a solution of *n*-butyl lithium (44ml, 2.5M solution in hexanes) was added dropwise over 10 minutes. The mixture was stirred for 0.5 hour, allowed to warm to –20°C then formaldehyde gas was bubbled through the mixture until no starting

material remained, as determined by glc analysis. On complete reaction the mixture was treated with water, the ether phase separated and the aqueous phase was extracted with ethyl acetate (twice). The organic extracts were combined, washed with water (three times), dried over magnesium sulphate and evaporated under reduced pressure to give the required product (24.96g) as a pale yellow liquid.

^{1}H NMR ($CDCl_3$) δ: 0.00(12H, s); 0.46(4H, s); 1.32(6H, s); 4.10(2H, s).

Step 2

The product from Step 1 (24.96g) was treated with dilute aqueous hydrochloric acid (300ml) and stirred at ambient temperature for 0.5 hour. The mixture was washed with diethyl ether (twice), the aqueous phase was evaporated under reduced pressure, distilled with toluene (twice) to remove residual water and the residual solid obtained was triturated with hexane to give 4-amino-1-hydroxy-4-methylpent-2-yne hydrochloride (13.1g) as a cream coloured solid.

^{1}H NMR ($CDCl_3$) δ: 1.48(6H, s); 4.06(2H, s); 5.32(1H, s); 8.64(3H, s).

Stage 2: Preparation of 4-amino-1-*tert.*-butyldimethylsilyloxy-4-methylpent-2-yne.

4-Amino-1-hydroxy-4-methylpent-2-yne hydrochloride (4.40g) was dissolved in dry *N,N*-dimethylformamide (100ml) and triethylamine (4.44ml) was added. The suspension was stirred at ambient temperature for 10minutes, imidazole (4.93g) was added followed by *t*-butyldimethylsilyl chloride(5.24g) in dry *N,N*-dimethylformamide (40ml). The mixture was stirred at ambient temperature for 18 hours then diluted with water. The mixture was extracted with diethyl ether (three times) and the organic extracts were combined, washed with water (twice) then dried over magnesium sulphate and evaporated under reduced pressure to give the required product (6.88g) as a yellow liquid.

^{1}H NMR ($CDCl_3$) δ: 0.04(6H, s); 0.84(9H, s); 1.30(6H, s); 4.22(2H, s).

Stage 3: Preparation of 2-(6-quinolinyloxy)butyric acid.

Step 1: Preparation of methyl 2-(6-quinolinyloxy)butyrate

6-Hydroxyquinoline (25.1g), methyl 2-bromobutyrate (32.3g) and anhydrous potassium carbonate (23.0g) in dry *N,N*-dimethylformamide (100ml) were stirred at 100°C for 3 hours then stored at ambient temperature for 18 hours. The mixture was added to water, extracted with ethyl acetate (three times) and the extracts combined, washed with water (four times) then dried over magnesium sulphate. The solvent was evaporated under reduced pressure to give the required product (39.0g) as a red oil.

^1H NMR ($CDCl_3$) δ: 1.10-1.14(3H, t); 2.04-2.12(2H, q); 3.78(3H, s); 4.72-4.76(1H, t); 7.00(1H, d); 7.36-7.40(1H, m); 7.42-7.46(1H, m); 8.02-8.04(2H, d); 8.80(1H, d).

Step2: Preparation of 2-(6-quinolinyloxy)butyric acid.

The product from Step 1 (38.8g) was stirred in a solution of sodium hydroxide (12.6g) in water (100ml) and heated to 90°C for 3 hours then cooled to ambient temperature. The solution was diluted with water and the aqueous phase was washed with ethyl acetate (twice), acidified to pH6 with aqueous hydrochloric acid then extracted with ethyl acetate (three times). The extracts were combined, dried over magnesium sulphate and the solvent evaporated under reduced pressure and the residue was washed with hexane to give the required product, 8.1g, as a yellow brown solid. The aqueous phase was re-extracted with ethyl acetate and processed as before to provide further required product (3.7g).

Stage 4

2-(6-Quinolinyloxy)butyric acid (0.61g), 4-amino-1-*tert*-butyldimethylsilyloxy-4-methylpent-2-yne (0.57g) and 4-dimethylaminopyridine (0.010g) in dry dichloromethane (10ml) were stirred and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.53g) was added. The mixture was stirred at ambient temperature for 3.5 hours, stored for 2 days, diluted with dichloromethane, washed with saturated aqueous sodium hydrogen carbonate (twice) and then with water. The organic phase was dried over magnesium sulphate and evaporated under reduced pressure to give a yellow oil. The oil was fractionated by chromatography (silica; hexane/ethyl acetate, 3:1 by volume) to give a gum that was triturated with hexane to give the required product (0.12g) as a colourless solid, m.p.78-80°C.

^1H NMR ($CDCl_3$) δ: 0.08(6H, s); 0.88(9H, s); 1.06-1.10(3H, t); 1.62-1.66(6H, d); 2.00-2.10(2H, m); 4.28(2H, s); 4.54-4.58(1H, t); 6.44(1H, s); 7.10(1H, s); 7.36-7.44(2H, m); 8.02-8.06(2H, d); 8.80(1H, m).

The hexane washings were evaporated under reduced pressure to give an oil (0.53g) containing further required product.

EXAMPLE 3

This Example illustrates the preparation of 2-(6-quinolinyloxy)-*N*-(1-hydroxy-4-methylpent-2-yn-4-yl) butyramide (Compound No. 10 of Table1)

2-(6-Quinolinyloxy)-N-(1-tert.butyldimethylsilyloxy-4-methylpent-2-yn-4-yl)butyramide (0.58g) in tetrahydrofuran (10ml) was stirred at 3-5°C and a solution of tetra *n*-butylammonium fluoride (2.64ml of 1M solution in tetrahydrofuran) was added dropwise over 5 minutes. On completion of addition, the mixture was stirred for 0.5 hour at 0°C, 0.75 hour at ambient temperature then stored for 18 hours. The solvent was evaporated under reduced pressure and the residue partitioned between ethyl acetate and aqueous ammonium chloride. The organic phase was separated, washed with aqueous ammonium chloride, brine, dried over magnesium sulphate and evaporated under reduced pressure to give a gum that was fractionated by chromatography (silica; hexane/ethyl acetate, 1:2 by volume) to give the required product as a colourless glass (0.30g).

^{1}H NMR ($CDCl_3$) δ: 1.06-1.10(3H, t); 1.58(3H, s); 1.60(3H, s); 1.98-2.08(3H, m); 4.22-4.24(2H, d); 4.56-4.60(1H, t); 6.42(1H, s); 7.10(1H, s); 7.36-7.44(2H, m); 8.04-8.08(2H, d); 8.80(1H, m).

EXAMPLE 4

This Example illustrates the preparation of 2-(6-quinolinyloxy)-*N*-(1-methoxy-4-methylpent-2-yn-4-yl)butyramide (Compound No. 12 of Table 1)

Step 1: Preparation of 4-amino-1-methoxy-4 methylpent-2-yne hydrochloride.

To a stirred suspension of sodium hydride (0.45g, 80% dispersion in mineral oil) in dry *N,N*-dimethylformamide (2ml) under an atmosphere of nitrogen at ambient temperature was added dropwise over 5 minutes a solution of 4-amino-1-hydroxy-4-methylpent-2-yne hydrochloride (0.75g) in dry *N,N*-dimethylformamide (20ml). The mixture was stirred for 2.75 hours at ambient temperature then a solution of methyl iodide (0.78g) in *N,N*-dimethylformamide (5ml) was added. The reaction was stirred for 2.5 hours, stored for 18 hours then poured into water, extracted with diethyl ether (three times) and the organic extracts were combined. The combined organic phase was extracted with dilute hydrochloric acid (three times) and the aqueous acidic extracts were combined and evaporated under reduced pressure. The residual solid was dried by evaporating under reduced pressure with toluene (twice) to give a yellow gum (0.8g) containing the required product. The compound was characterised from its NMR spectrum.

^{1}H NMR ($CDCl_3$) δ: 1.78(6H, s); 3.40(3H, s); 4.12(2H, s); 8.90(3H, br s).

Step 2

Triethylamine (0.54ml) was added to a stirred solution of the product from Step 1 (0.8g) in dry *N,N*-dimethylformamide (10ml). The solution was stirred for 5 minutes then 1-hydroxybenzotriazole (0.39g) and *N*-(3-dimethylaminopropyl)-*N'*-ethyl carbodiimide hydrochloride (0.55g) in dry *N,N*-dimethylformamide (5ml) were added. The mixture was stirred at ambient temperature for 2 hours, poured into water and the aqueous phase extracted with ethyl acetate (three times). The organic extracts were combined, washed with water (three times), dried over magnesium sulphate and evaporated under reduced pressure to give a red oil. The oil was fractionated by chromatography (silica; ethyl acetate) to give the required product (0.15g) as a pale yellow gum.

^{1}H NMR ($CDCl_3$) δ: 1.06-1.12(3H, t); 1.62(6H, s); 2.00-2.08(2H, m); 3.32(3H, s); 4.08-4.24(2H, s); 4.58-4.62(1H, t); 6.44(1H, s); 7.10(1H, m); 7.36-7.46(2H, m); 8.04-8.08(2H, d); 8.82(1H, m).

EXAMPLE 5

This Example illustrates the preparation of 2-(6-quinolinyloxy)-2-(ethoxy)-*N*-(2-methylpent-3-yn-2-yl) acetamide (Compound No. 2 of Table 17)

Step 1: Preparation of ethyl 2-(6-quinolinyloxy)-2-(ethoxy)acetate.

Potassium t-butoxide (3.15g) was dissolved in t-butyl alcohol (20ml) and stirred for 10 minutes at ambient temperature. 6-Hydroxyquinoline (3.0g) was added, the resulting dark green solution was stirred for 15 minutes, and then ethyl 2-chloro-2-ethoxyacetate (4.22g, 90% pure) added, followed by a catalytic amount of potassium iodide (0.005g). The mixture was stirred for 18 hours, poured into water and extracted with chloroform. The organic fraction was washed with brine, water, and dried over magnesium sulphate. The solvent was evaporated to give a brown oil, which was purified by flash chromatography on silica gel, eluting with a gradient of ethyl acetate:hexane (1:2 to 4:1) to give ethyl 2-(6-quinolinyloxy)-2-(ethoxy)acetate as a pale brown oil (3.68g).

^{1}H NMR ($CDCl_3$) δ ppm: 1.28 (3H, t); 1.31 (3H, t); 3.79 (1H, m); 3.90 (1H, m); 4.31 (2H, q); 5.68 (1H, s); 7.38 (2H, dd); 7.51 (1H, dd); 8.06 (2H, dd); 8.32 (1H, dd).

Step 2: Preparation of 2-(6-quinolinyloxy)-2-(ethoxy)acetic acid.

Ethyl 2-(6-quinolinyloxy)-2-(ethoxy)acetate (3.68g) was added to a solution of sodium hydroxide (0.589g) in water (10ml) and methanol (30ml) and stirred for 5 minutes. The solution was evaporated under reduced pressure, water added and the

aqueous phase was washed with ethyl acetate. The aqueous phase was acidified with hydrochloric acid and extracted with ethyl acetate. The extracts were combined, dried over magnesium sulphate and evaporated under reduced pressure to give 2-(6-quinolinyloxy)-2-(ethoxy)acetic acid (1.47g) as a cream solid.

^{1}H NMR ($CDCl_3$) δ ppm: 1.33 (3H, t); 3.98 (1H, m); 5.71 (1H, s); 7.44 (1H, dd); 7.52 (2H, m); 8.05 (1H, d); 8.20 (1H, d); 8.84 (1H, dd).

Step 3

Triethylamine (0.3ml) was added to a stirred solution of 4-amino-4-methylpent-2-yne hydrochloride (0.054g) in *N,N*-dimethylformamide (2 ml) giving a white suspension. 2-(6-Quinolinoxy)-2-(ethoxy)acetic acid (0.1g) was added followed by *N*-(3-dimethylaminopropyl)-*N'*-ethyl carbodiimide hydrochloride (0.077g) and a catalytic amount of 1-hydroxybenzotriazole (0.005g), and the white suspension was stirred at ambient temperature for 18 hours. Water was added and the aqueous phase was extracted with ethyl acetate. The organic phase was washed with water, saturated aqueous sodium bicarbonate and brine, dried over magnesium sulphate and evaporated under reduced pressure to give a yellow oil (0.117 g). The oil was purified by flash chromatography (silica gel; ethyl acetate/hexane, 1:1 by volume) to give the required product (0.096g) as a colourless oil.

^{1}H NMR ($CDCl_3$) δ ppm: 1.28 (3H, t); 1.64 (3H, s); 1.66 (3H, s); 1.80 (3H, s); 3.70 (1H, m); 3.88 (1H, m); 5.48 (1H, s); 6.79 (1H, bs); 7.37 (1H, dd); 7.49 (1H, d); 7.52 (1H, dd); 8.05 (1H, d); 8.08 (1H, d); 8.82 (1H, dd).

EXAMPLE 6

This Example illustrates the preparation of 2-(6-quinolinyloxy)- *N*-(2-methylpent-3-yn-2-yl)-3-methoxypropionamide (Compound No. 2 of Table 11)

Stage 1: Preparation of 2-bromo-*N*-(4-methylpent-2-yn-4-yl) 3-methoxypropionamide.

Step1: Preparation of methyl 2-bromo-3-methoxypropionate

Methyl 2,3-dibromopropionate (21.9g) and trimethylamine *N*-oxide (0.1g) in methanol (8ml) were cooled to –5°C with stirring under an atmosphere of nitrogen. A methanolic solution of sodium methoxide, freshly prepared from sodium (2.25g) and methanol (24ml), was added dropwise over 15 minutes to the mixture, which was maintained below 0°C by cooling. On complete addition, the mixture was stirred for a further 30 minutes then acetic acid (1ml) was added followed by diethyl ether (100ml).

The mixture was filtered to remove insoluble salts and the filtrate evaporated under reduced pressure to give an oil, which was re-dissolved in a small volume of diethyl ether and re-filtered. The filtrate was evaporated under reduced pressure to give the required product (17.4g) as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ: 3.41(3H, s); 3.74(1H, dd); 3.82(3H, s); 3.92(1H, dd); 4.34(1H, dd).

Step 2: Preparation of 2-bromo-3-methoxypropionic acid.

Methyl 2-bromo-3-methoxypropionate (1.00g) in tetrahydrofuran (8ml) was stirred at 10°C and lithium hydroxide monohydrate (0.21g) in water (1.5ml) was added dropwise. On complete addition, the mixture was stirred for 1.5 hours, the colourless solution was evaporated under reduced pressure to a small volume then the aqueous solution was taken to pH 3 with dilute sulphuric acid. The mixture was extracted with diethyl ether (50ml) and the organic phase separated, washed with brine, dried over magnesium sulphate then evaporated under reduced pressure to give the required product (0.6g) as a colourless liquid.

^{1}H NMR ($CDCl_3$) δ: 3.45(3H, s); 3.78(1H, m); 3.92(1H, m); 4.38(1H, m); 6.65(1H, br s).

Step 3: Preparation of 2-bromo-*N*-(4-methylpent-2-yn-4-yl) 3-methoxypropionamide.

2-Bromo-3-methoxypropionic acid (0.366g) was dissolved in dry dichloromethane (4ml) containing dry *N,N*-dimethylformamide (0.05ml) with stirring and oxalyl chloride (0.254g) was added. The mixture was stirred at ambient temperature for 2 hours then evaporated under reduced pressure to give 2-bromo-3-methoxypropionic acid chloride (C=O, ν 1780cms^{-1}). The acid chloride was dissolved in dry dichloromethane (6ml) and 4-amino-4-methylpent-2-yne hydrochloride (0.267g) was added then the mixture was cooled to 3°C and triethylamine (0.404g) was added dropwise, keeping the reaction temperature between 0-5°C. The suspension that had formed was stirred at ambient temperature for 1 hour, diluted with further dichloromethane, washed with hydrochloric acid (2M) and the organic phase separated, dried over magnesium sulfate then evaporated under reduced pressure to give a gum. The gum was fractionated by chromatography (silica: hexane/ethyl acetate, 3:2 by volume) to give the required product (0.3g) as a colourless solid.

^{1}H NMR ($CDCl_3$) δ: 1.63(6H, s); 1.82(3H, s); 3.44(3H, s); 3.88(2H, m); 4.32(1H, m); 6.62(1H, s).

Stage 2

6-Hydroxyquinoline (0.083g), anhydrous potassium carbonate (0.087g) and 2-bromo-*N*-(4-methylpent-2-yn-4-yl) 3-methoxypropionamide (0.150g) in dry *N,N*-dimethylformamide (3ml) were stirred and heated to 80°C for 5 hours then stored for 72 hours at ambient temperature. The yellow suspension was diluted with water, extracted with ethyl acetate and the organic phase was separated then washed with water, dried over magnesium sulphate and evaporated under reduced pressure to a gum. The gum was fractionated by chromatography (silica; ethyl acetate: hexane, 3:2 by volume) to give the required product (0.055g) as a colourless gum.

^{1}H NMR ($CDCl_3$) δ: 1.58(3H, s); 1.60(3H, s); 1.78(3H, s); 3.46(3H, s); 3.95(2H, m); 4.78(1H, m); 6.60(1H, s); 7.18(1H, m); 7.40(1H, m); 7.50(1H, m); 8.08(2H, m); 8.83(1H, m).

EXAMPLE 7

This Example illustrates the preparation of 2-(6-quinazolinoxy)-*N*-(4-methylpent-2-yn-4-yl) butyramide (Compound No.2 of Table 20)

6-Hydroxyquinazoline (0.060g, prepared as described in *J. Chem. Soc.* (1952), 4985) and 2-bromo-*N*-(4-methylpent-2-yn-4-yl) butyramide (0.101g) were dissolved in dry *N,N*-dimethylformamide (2ml) containing anhydrous potassium carbonate (0.088g). The mixture was stirred and heated to 80°C for 5 hours then allowed to cool to ambient temperature and stored for 18 hours. The brown suspension was diluted with water, extracted into ethyl acetate and the organic phase separated, washed with water, dried over magnesium sulphate and evaporated under reduced pressure to give a pale brown oil. The oil was fractionated by chromatography (silica; ethyl acetate/hexane, 4:1 by volume) to give the title product (0.12g) as a pale brown gum.

^{1}H NMR ($CDCl_3$) δ: 1.04(3H, t); 1.53(6H, s); 1.72(3H, s); 1.95-2.05(2H, m); 4.54(1H, m); 6.30(1H, s); 7.14(1H, m); 7.60(1H, dd); 7.97(1H, d); 9.20(1H, s); 9.25(1H, s).

EXAMPLE 8

In a similar procedure to Example 1, 7-hydroxyisoquinoline (commercially available) and 2-bromo-*N*-(4-methylpent-2-yn-4-yl) butyramide were reacted to give 2-(7-isoquinolinyloxy)-*N*-(4-methylpent-2-yn-4-yl) butyramide (Compound No. 2 of Table 39) as a colourless solid, m.p. 149-150°C.

^{1}H NMR ($CDCl_3$) δ: 1.08(3H, t); 1.58(3H, s); 1.59(3H, s); 1.77(3H, s); 1.98-2.12(2H, m); 4.58(1H, m); 6.40(1H, s); 7.26(1H, d); 7.42(1H, dd); 7.61(1H, d); 7.79(1H, d); 8.45(1H, d); 9.14(1H, s).

EXAMPLE 9

In a similar procedure to Example 6, 7-hydroxyisoquinoline (commercially available) and 2-bromo-*N*-(4-methylpent-2-yn-4-yl) 3-methoxypropionamide were reacted to give 2-(7-isoquinolinyloxy)- *N*-(2-methylpent-3-yn-2-yl)-3-methoxypropionamide (Compound No. 2 of Table 49) as a colourless solid, m.p.155-156°C.

^{1}H NMR ($CDCl_3$) δ: 1.59(3H, s); 1.60(3H, s); 1.77(3H, s); 3.45(3H, s); 3.88-3.96(2H, m); 4.78(1H, m); 6.54(1H, s); 7.31(1H, d); 7.47(1H, dd); 7.61(1H, d); 7.80(1H, d); 8.46(1H, d); 9.14(1H, s).

EXAMPLE 10

This Example illustrates the preparation of 2-(3-bromo-6-quinolinyloxy)-*N*-(4-methylpent-2-yn-4-yl) butyramide (Compound No. 2 of Table 77) and 2-(3,8-dibromo-6-quinolinyloxy)-*N*-(4-methylpent-2-yn-4-yl) butyramide (Compound No. 2 of Table 115)

Stage 1: Preparation of 3-bromo-6-hydroxyquinoline and 3,8-dibromo-6-hydroxy-quinoline

Step 1: Preparation of 3-bromo-6-nitroquinoline and 3,8-dibromo-6-nitroquinoline

In a modification of the procedure described in *Liebigs Ann Chem*, (1966), 98-106 to make 3-bromo-6-nitroquinoline, 6-nitroquinoline (5.5g) in carbon tetrachloride (200ml) containing pyridine (5.0g) was treated with bromine (15.3g) and heated to reflux until all the 6-nitroquinoline had reacted. The reaction mixture was cooled to ambient temperature, stored for 18 hours then partitioned between chloroform and hydrochloric acid (2M). The mixture was filtered and the organic phase was separated, washed with saturated aqueous sodium hydrogen carbonate, dried over magnesium sulphate then evaporated under reduced pressure to give a pale yellow solid. The solid was recrystallised from glacial acetic acid to give a mixture containing 3-bromo-6-nitroquinoline (4 parts) and 3,8-dibromo-6-nitroquinoline (1 part) as a pale yellow solid (4.06g).

Step 2: Preparation of 6-amino-3-bromoquinoline and 6-amino-3,8-dibromoquinoline

The product from Step 1 (4.0g) was suspended in a mixture of propan-2-ol (15ml), water (8ml) and concentrated hydrochloric acid (0.5ml) at ambient temperature with stirring. To the mixture was added iron powder (6.0g) in portions resulting in an exothermic reaction producing a dark red suspension. The suspension was cooled to ambient temperature, extracted into aqueous hydrochloric acid (2M), filtered and washed with diethyl ether. The aqueous acidic phase was separated, made basic with aqueous sodium hydroxide (2M) and the thick precipitate that was produced was extracted with ethyl acetate (twice). The extracts were combined, washed with brine then dried over magnesium sulphate and evaporated under reduced pressure to give a pale brown solid. The solid was fractionated by chromatography (silica) eluting first with dichloromethane to provide 6-amino-3,8-dibromoquinoline, 0.15g (MH^+ 301, 2x Br) then with hexane/ethyl acetate (1:1 by volume) to give 6-amino-3-bromoquinoline, 1.0g, m.p.151-2°C (MH^+ 223, 1x Br).

Step 3: Preparation of 3,8-dibromo-6-hydroxyquinoline

6-Amino-3,8-dibromoquinoline (0.15g) was suspended in phosphoric acid (75%, 11 ml) and heated in a sealed glass tube at 180°C for 72 hours. The mixture was allowed to cool to ambient temperature, diluted with ice (50ml) and taken to pH 2 with aqueous sodium hydroxide (4M). The brown suspension that formed was extracted with ethyl acetate (twice), dried over magnesium sulphate then evaporated under reduced pressure to give 3,8-dibromo-6-hydroxyquinoline (M^+-H 300, 2x Br) as a dark red solid that was used in the next stage without further purification, ^{1}H NMR (*d6* DMSO) δ: 7.14(1H, d); 7.60(1H, d); 8.52(1H, d); 8.71(1H, d).

In a similar procedure to Step 3, 6-amino-3-bromoquinoline was converted to 3-bromo-6-hydroxyquinoline, brown solid, ^{1}H NMR (*d6* DMSO) δ: 7.19(1H, d); 7.40(1H, dd); 7.92(1H, d); 8.66(1H, s); 8.79(1H, s).

Stage 2: Preparation of 2-(3-bromo-6-quinolinyloxy)-*N*-(4-methylpent-2-yn-4-yl) butyramide

To a stirred mixture of 3-bromo-6-hydroxyquinoline (0.179g) and anhydrous potassium carbonate (0.121g) in dry *N,N*-dimethylformamide (2ml) at 80°C was added 2-bromo-*N*-(4-methylpent-2-yn-4-yl) butyramide (0.197g) and the reaction maintained at this temperature for 15 hours. The brown suspension produced was cooled to ambient

temperature, poured into water and extracted with diethyl ether. The extract was washed with water, dried over magnesium sulphate then evaporated under reduced pressure to give a brown gum. The gum was fractionated by chromatography (silica; hexane/ethyl acetate) to give 2-(3-bromo-6-quinolinyloxy)-*N*-(4-methylpent-2-yn-4-yl) butyramide (0.125g) as a colourless solid, m.p. 109-112°C, ^{1}H NMR ($CDCl_3$) δ: 1.08(3H, t); 1.58 (3H, s); 1.59(3H, s); 1.77(3H, s); 1.99-2.06(2H, m); 4.54(1H, t); 6.37(1H, s); 7.02(1H, m); 7.42(1H, dd); 8.02(1H, d); 8.19(1H, m); 8.78(1H,m).

In a similar procedure, 3,8-dibromo-6-hydroxyquinoline was reacted with 2-bromo-*N*-(4-methylpent-2-yn-4-yl) butyramide to give 2-(3,8-dibromo-6-quinolinyloxy)-*N*-(4-methylpent-2-yn-4-yl) butyramide as a colourless gum, ^{1}H NMR ($CDCl_3$) δ: 1.07(3H, t);1.59 (3H, s); 1.60(3H, s); 1.78(3H, s); 1.99-2.06(2H, m); 4.52(1H, t); 6.30(1H, s); 7.00(1H, m); 7.82(1H, dd); 8.21(1H, d); 8.88(1H, m).

EXAMPLE 11

This Example illustrates the preparation of 2-(3-chloro-6-quinolinyloxy)-*N*-(4-methyl-pent-2-yn-4-yl) butyramide (Compound No. 2 of Table 58)

Stage 1: Preparation of 3-chloro-6-hydroxyquinoline

3-Bromo-6-hydroxyquinoline (2.75g) and cuprous chloride (9g) in dry *N*-methylpyrrolidin-2-one (25ml) were stirred and heated at 150°C under an atmosphere of nitrogen for 2 hours. The dark red suspension was cooled to ambient temperature, poured into water then treated with sufficient aqueous ammonia to dissolve the solid material. The blue solution was taken to pH 5-6 with hydrochloric acid (2M) then ethyl acetate was added. The mixture was filtered and the insoluble solids washed with ethyl acetate. The organic component of the filtrate was separated and the aqueous phase was further extracted with ethyl acetate. The ethyl acetate fractions were combined, washed with brine, dried over magnesium sulphate then evaporated under reduced pressure to give a solid. The solid was fractionated by chromatography (silica; hexane/ethyl acetate, 2:1 by volume) to give 3-chloro-6-hydroxyquinoline as a pale yellow solid, 0.95g. (M^+179, 1xCl). ^{1}H NMR ($CDCl_3$) δ: 7.06(1H, d); 7.35(1H, dd); 7.91(1H, d); 7.96(1H, d); 8.59(1H, d); 9.55(1H, s).

Stage 2

To a stirred mixture of 3-chloro-6-hydroxyquinoline (0.130g) and anhydrous potassium carbonate (0.110g) in dry *N,N*-dimethylformamide (3ml) at 80°C was added 2-

bromo-*N*-(4-methylpent-2-yn-4-yl) butyramide (0.197g) and the reaction maintained at this temperature for 6 hours. The brown suspension produced was cooled to ambient temperature, poured into water and extracted with diethyl ether. The extract was washed with water, dried over magnesium sulphate then evaporated under reduced pressure to give a brown gum. The gum was fractionated by chromatography (silica; hexane/ethyl acetate 4:1 by volume) to give 2-(3-chloro-6-quinolinyloxy)-*N*-(4-methylpent-2-yn-4-yl) butyramide (0.167g) as a colourless solid, m.p. 105-107°C, ^{1}H NMR ($CDCl_3$) δ: 1.08(3H, t); 1.58 (3H, s); 1.59(3H, s); 1.77(3H, s); 1.99-2.08(2H, m); 4.55(1H, t); 6.37(1H, s); 7.02(1H, d); 7.41(1H, dd); 8.01(1H, d); 8.02(1H, d); 8.70(1H, m); 8.78(1H,m).

EXAMPLE 12

This Example illustrates the preparation of 2-(6-quinolinyloxy)-*N*-(1-methoxy-4-methylpent-2-yn-4-yl) 3-methoxypropionamide (Compound No. 12 of Table 11) and 2-(3-bromo-6-quinolinyloxy)-*N*-(1-methoxy-4-methylpent-2-yn-4-yl) 3-methoxy-propionamide (Compound No. 12 of Table 87)

Stage 1: Preparation of 2-bromo-*N*-(1-methoxy-4-methylpent-2-yn-4-yl) 3-methoxy-propionamide

2-Bromo-3-methoxypropionic acid (0.51g) was dissolved in dry dichloromethane (10ml) containing dry *N,N*-dimethylformamide (0.05ml) with stirring and oxalyl chloride (0.36g) was added. The mixture was stirred at ambient temperature for 2 hours then evaporated under reduced pressure to give 2-bromo-3-methoxypropionic acid chloride (C=O, ν 1780cms^{-1}). The acid chloride was dissolved in dry dichloromethane (5ml) and added to 4-amino-1-methoxy-4-methylpent-2-yne hydrochloride (0.46g) in dry dichloromethane (10ml) at 0°C with stirring. Triethylamine (0.78ml) was added dropwise, while keeping the reaction temperature between 4-9°C. The suspension that had formed was stirred at ambient temperature for 2 hours, stored at ambient temperature for 18 hours, diluted with further dichloromethane and washed with aqueous sodium hydrogen carbonate then water (twice). The organic phase was separated, dried over magnesium sulphate and evaporated under reduced pressure to give a gum. The gum was fractionated by chromatography (silica: hexane/ethyl acetate) to give the required product (0.36g) as a colourless oil, ^{1}H NMR ($CDCl_3$) δ: 1.66(6H, s); 3.38(3H, s); 3.44(3H, s); 3.82-3.90(2H, q); 4.12(2H, s); 4.30-4.32(1H, t); 6.62(1H, s).

Stage 2

In a similar procedure to Example 6 Stage 2, 6-hydroxyquinoline was reacted with 2-bromo-*N*-(1-methoxy-4-methylpent-2-yn-4-yl) 3-methoxypropionamide to give 2-(6-quinolinyloxy)-*N*-(1-methoxy-4-methylpent-2-yn-4-yl) 3-methoxypropionamide as a colourless oil. ^{1}H NMR ($CDCl_3$) δ: 1.60(3H, s); 1.62(3H, s); 3.34(3H, s); 3.44(3H, s); 3.90-3.94(2H, m); 4.06(2H, s); 4.76-4.80(1H, m); 6.60(1H, s); 7.14-7.16(1H, m); 7.36-7.40(1H, m); 7.46-7.50(1H, m); 8.04-8.08(2H, d); 8.82-8.84(1H, m).

Stage 3

In a similar procedure to Example 6 Stage 2, 3-bromo-6-hydroxyquinoline was reacted with 2-bromo-*N*-(1-methoxy-4-methylpent-2-yn-4-yl) 3-methoxypropionamide to give 2-(3-bromo-6-quinolinyloxy)-*N*-(1-methoxy-4-methylpent-2-yn-4-yl) 3-methoxypropionamide as a gum. ^{1}H NMR ($CDCl_3$) δ: 1.58(3H, s); 1.59(3H, s); 1.77(3H, s0; 3.44(3H, s); 3.87-3.95(2H, m); 4.73(1H, m); 6.52(1H, s); 7.08(1H, m); 7.48(1H, dd); 8.02(1H, d); 8.21(1H, m); 8.79(1H, m).

EXAMPLE 13

This Example illustrates the preparation of 2-(6-quinolinyloxy)-*N*-(4-methylpent-2-yn-4-yl) butyramide 1-oxide (Compound No. 2 of Table 134)

2-(6-Quinolinyloxy)-*N*-(4-methylpent-2-yn-4-yl) butyramide (1.0g) in dichloromethane (25ml) was cooled to 0°C with stirring and 3-chloroperbenzoic acid (1.21g, 50%) was added in portions then stirred for a further 15 minutes at 0°C followed by 1.5 hours at ambient temperature. The mixture was washed with aqueous sodium hydrogen carbonate (three times), water (twice), dried over magnesium sulphate then evaporated under reduced pressure to give a gum which was triturated with diethyl ether to give the required product as a pale brown solid, 0.75g, m.p. 140-143°C, ^{1}H NMR ($CDCl_3$) δ: 1.06-1.10(3H, t); 1.56(3H, s); 1.58(3H, s); 1.76(3H, s); 2.00-2.08(2H, m); 4.56(1H, t); 6.32(1H, s); 7.14 (1H, m); 7.28-7.30(1H, d); 7.44-7.46(1H, d); 7.62-7.64(1H,d); 8.42-8.44(1H, d); 8.70-8.72(1H, d).

EXAMPLE 14

This Example illustrates the preparation of 2-(3-cyano-6-quinolinyloxy)-*N*-(4-methylpent-2-yn-4-yl) butyramide (Compound No. 2 of Table 96)

Stage 1: Preparation of 3-cyano-6-hydroxyquinoline [reference *Liebigs Ann Chem* (1966), 98-106]

3-Bromo-6-hydroxyquinoline (1.12g) in dry *N*-methylpyrrolidin-2-one (10ml) was treated with cuprous cyanide (0.55g) and stirred at 150°C for 7 hours under an atmosphere of nitrogen then stored at ambient temperature for 18 hours. The mixture was treated with sodium cyanide (1.5g) in water (5ml) and heated at 75°C for 15 minutes. 10% Aqueous ammonium chloride solution (25ml) was added and the mixture cooled to ambient temperature. The reaction mixture was extracted with ethyl acetate and the organic phase separated, washed with water, dried over magnesium sulphate and evaporated under reduced pressure to give a yellow brown solid. The solid was fractionated by chromatography to give the required product as a yellow solid.

Stage 2

In a similar procedure to Example 6 Stage 2, 3-cyano-6-hydroxyquinoline was reacted with 2-bromo-*N*-(4-methylpent-2-yn-4-yl) butyramide to give 2-(3-cyano-6-quinolinyloxy)-*N*-(4-methylpent-2-yn-4-yl) butyramide as a pale yellow solid, m.p.116-118°C, ^{1}H NMR ($CDCl_3$) δ: 1.08(3H, t); 1.61(3H, s); 1.63(3H, s); 1.80(3H, s); 2.07-2.13(2H, m); 4.72(1H, t); 6.46(1H, s); 7.50 (1H, m); 7.57(1H, dd); 7.71(1H, d); 8.17(1H,d); 8.92(1H, d).

EXAMPLE 15

This Example illustrates the preparation of 2-(3-bromo-6-quinolinyloxy)-*N*-(1-cyano-6-methylhept-4-yn-6-yl) butyramide (Compound No. 90 of Table 77) and 2-(3-bromo-6-quinolinyloxy)-*N*-(1-chloro-6-methylhept-4-yn-6-yl) butyramide (Compound No. 91 of Table 77)

Stage 1: The preparation of 2-bromo-*N*-(1-chloro-6-methylhept-4-yn-6-yl) butyramide

Step 1: Preparation of 6-(1-chloro-6-methylhept-4-yn-6-yl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane

n-Butyl lithium (97.6ml, 2.5M in hexanes) was added dropwise over 0.5 hours to a stirred solution of 1-(1,1-dimethyl-2-propynyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane (55.1g) in dry tetrahydrofuran (450ml) under an atmosphere of nitrogen at –70°C. The mixture was stirred for 1.5 hours at –70°C, allowed to warm to –15°C then a solution of 1-chloro-3-iodopropane (55.0g) in dry tetrahydrofuran (50ml) was added dropwise over 20 minutes whilst allowing the reaction temperature to slowly warm to 0°C. On complete addition, the reaction mixture was stirred at ambient

temperature for 4.25 hours then stored for 18 hours. The mixture was diluted with water and extracted with ethyl acetate (twice). The extracts were combined, washed with water (three times), dried over magnesium sulphate then evaporated under reduced pressure to give the required product as an orange liquid, 78.5g, ^{1}H NMR ($CDCl_3$) δ: 0.00(12H,s); 0.46(4H, s); 1.30(6H, s); 1.76(2H, m); 2.18(2H, t); 2.46(2H, t).

Step 2: Preparation of 1-chloro-6-methylhept-4-yn-6-ylamine hydrochloride

The product from Step 1 (78.5g) was stirred at –5°C and dilute aqueous hydrochloric acid (785ml, 2M) was added slowly whilst maintaining the reaction temperature below 30°C during the addition. On complete addition, the mixture was stirred for a further 1 hour at ambient temperature, washed with diethyl ether (twice), evaporated under reduced pressure and the residual water removed by azeotropic distillation with toluene. The solid obtained was dissolved in dichloromethane, dried over magnesium sulphate and evaporated under reduced pressure to give the required product as a cream coloured solid, 36.5g, ^{1}H NMR ($CDCl_3$) δ: 1.74(6H, s); 1.97(2H, m); 2.39(2H, m); 3.68(2H, t); 8.80(3H, broad s).

Step 3: The preparation of 2-bromo-*N*-(1-chloro-6-methylhept-4-yn-6-yl) butyramide

The product from Step 2 (12.2g) was suspended in dry dichloromethane (300ml), cooled to 5°C with stirring and dry triethylamine (18.1ml) was added. The mixture was stirred for 0.25 hours and 2-bromobutyryl bromide (14.3g) in dichloromethane (25ml) was added dropwise over 0.5 hours at 10-18°C. The mixture was stirred for a further 0.5 hours then allowed to warm to ambient temperature for 2 hours and stored for 18 hours. Water was added and the organic phase was separated, washed with water (three times), dried over magnesium sulphate then evaporated under reduced pressure to give the required product as a dark yellow oil, 17.4g, ^{1}H NMR ($CDCl_3$) δ: 1.04(3H, t); 1.62(6H, s); 1.96(2H, m); 2.10(2H, m); 2.38(2H, m); 3.66(2H, t); 4.12(1H, t); 6.44(1H, s).

Stage 2

In a similar procedure to Example 6 Stage 2, 3-bromo-6-hydroxyquinoline was reacted with 2-bromo-*N*-(1-chloro-6-methylhept-4-yn-6-yl) butyramide to give 2-(3-bromo-6-quinolinyloxy)-*N*-(1-chloro-6-methylhept-4-yn-6-yl) butyramide as a colourless oil. ^{1}H NMR ($CDCl_3$) δ: 1.04-1.10(3H, t); 1.60(6H, s); 1.86-1.94(2H, m); 2.00-2.06(2H, m); 2.32-2.36(2H, t); 3.60-3.64(2H, t); 4.56(1H, t); 6.34(1H, s); 7.02 (1H, m); 7.42-7.46(1H, dd); 8.03 (1H, d); 8.22(1H, s); 8.78(1H, s).

Stage 3

The product from Stage 2 (0.19g) was dissolved in dry *N,N*-dimethylformamide (4ml) containing potassium cyanide (0.056g) with stirring and heated to 100°C for 6 hours then cooled to ambient temperature and stored for 2 days. The mixture was diluted with water and extracted with ethyl acetate (three times). The extracts were combined, washed with water (twice), dried over magnesium sulphate and evaporated under reduced pressure to give a yellow gum. The gum was fractionated by chromatography (silica; hexane/ethyl acetate, 1:1 by volume) to give 2-(3-bromo-6-quinolinyloxy)-*N*-(1-cyano-6-methylhept-4-yn-6-yl) butyramide as a yellow gum, 0.080g, ^{1}H NMR ($CDCl_3$) δ: 1.04-1.10(3H, t); 1.56(6H, s); 1.78-1.84(2H, m); 2.00-2.08(2H, m); 2.32-2.36(2H, t); 2.48-2.52(2H, t); 4.58(1H, t); 6.36(1H, s); 7.02 (1H, d); 7.40-7.44(1H, dd); 8.02(1H, d); 8.22(1H, s); 8.80(1H, s).

EXAMPLE 16

This Example illustrates the fungicidal properties of compounds of formula (1).

The compounds were tested in a leaf disk assay, with methods described below. The test compounds were dissolved in DMSO and diluted into water to 200 ppm. In the case of the test on *Pythium ultimum*, they were dissolved in DMSO and diluted into water to 20 ppm.

Erysiphe graminis f.sp. hordei (barley powdery mildew): Barley leaf segments were placed on agar in a 24-well plate and sprayed with a solution of the test compound. After allowing to dry completely, for between 12 and 24 hours, the leaf disks were inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound was assessed four days after inoculation as preventive fungicidal activity.

Erysiphe graminis f.sp. tritici (wheat powdery mildew): Wheat leaf segments were placed on agar in a 24-well plate and sprayed with a solution of the test compound. After allowing to dry completely, for between 12 and 24 hours, the leaf disks were inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound was assessed four days after inoculation as preventive fungicidal activity.

Puccinia recondita f.sp. tritici (wheat brown rust): Wheat leaf segments were placed on agar in a 24-well plate and sprayed with a solution of the test compound. After allowing to dry completely, for between 12 and 24 hours, the leaf disks were inoculated with a

spore suspension of the fungus. After appropriate incubation the activity of a compound was assessed nine days after inoculation as preventive fungicidal activity.

Septoria nodorum (wheat glume blotch): Wheat leaf segments were placed on agar in a 24-well plate and sprayed with a solution of the test compound. After allowing to dry completely, for between 12 and 24 hours, the leaf disks were inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound was assessed four days after inoculation as preventive fungicidal activity.

Pyrenophora teres (barley net blotch): Barley leaf segments were placed on agar in a 24-well plate and sprayed with a solution of the test compound. After allowing to dry completely, for between 12 and 24 hours, the leaf disks were inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound was assessed four days after inoculation as preventive fungicidal activity.

Pyricularia oryzae (rice blast): Rice leaf segments were placed on agar in a 24-well plate and sprayed with a solution of the test compound. After allowing to dry completely, for between 12 and 24 hours, the leaf disks were inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound was assessed four days after inoculation as preventive fungicidal activity.

Botrytis cinerea (grey mould): Bean leaf disks were placed on agar in a 24-well plate and sprayed with a solution of the test compound. After allowing to dry completely, for between 12 and 24 hours, the leaf disks were inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound was assessed four days after inoculation as preventive fungicidal activity.

Phytophthora infestans (late blight of potato on tomato): Tomato leaf disks were placed on water agar in a 24-well plate and sprayed with a solution of the test compound. After allowing to dry completely, for between 12 and 24 hours, the leaf disks were inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound was assessed four days after inoculation as preventive fungicidal activity.

Plasmopara viticola (downy mildew of grapevine): Grapevine leaf disks were placed on agar in a 24-well plate and sprayed a solution of the test compound. After allowing to dry completely, for between 12 and 24 hours, the leaf disks were inoculated with a spore suspension of the fungus. After appropriate incubation the activity of a compound was assessed seven days after inoculation as preventive fungicidal activity.

Pythium ultimum (Damping off): Mycelial fragments of the fungus, prepared from a fresh liquid culture, were mixed into potato dextrose broth. A solution of the test compound in dimethyl sulphoxide was diluted with water to 20ppm then placed into a 96-well microtiter plate and the nutrient broth containing the fungal spores was added. The test plate was incubated at 24°C and the inhibition of growth was determined photometrically after 48 hours.

The following Compounds [Compound No (Table)] gave more than 60% control of the following fungal infections at 200ppm:

Phytophthora infestans: 2(1), 10(1), 12(1), 50(1), 2(20), 2(58), 2(77), 90(77), 91(77).

Plasmopara viticola: 2(1), 2(49), 2(58), 2(77), 90(77), 91(77), 2(96), 2(115).

Erysiphe graminis f.sp. hordei: 10(1),2(17).

Erysiphe graminis f.sp tritici: 10(1), 50(1), 2(77), 91(77), 2(115).

Botrytis cinerea: 2(77), 2(115).

Puccinia recondita f.sp. tritici: 90(77).

Septoria nodorum: 10(1).

Pyrenophora teres: 2(20).

The following Compounds gave more than 60% control of the following fungal infection at 20ppm:

Pythium ultimum: 2(1), 10(1), 12(1), 50(1), 2(11), 12(11), 2(17), 2 (20), 2(39), 2(49), 2(77), 90(77), 91(77), 2(115), 2(134).